



Brain Canada

Famille Chagnon

Chagnon Family - Brain Canada Request for Applications Multi-Investigator Research Initiative (MIRI)

Interventions for Prevention of Alzheimer Disease and Related Disorders

Purpose

Supported by the Chagnon Family and Brain Canada (Canada Brain Research Fund), the purpose of these MIRI grants is to accelerate novel and transformative intervention research that will improve the prevention of **Alzheimer Disease and Related Disorders** (“**ADRD**”). This initiative is meant to stimulate and reward “outside the box” ideas by supporting research that is truly innovative and may challenge standard paradigms, in order to accelerate the achievement of outcomes that will have a positive and meaningful impact for those at risk from ADRD. The ultimate goal is to prevent ADRD. Over the next five years, \$25 million will be provided by the Chagnon Family and by Brain Canada, through the Canada Brain Research Fund; additional funds in the subsequent five years may also be possible. This will be the largest investment in interventions for prevention of ADRD ever made in this country and sets forth a challenge to fast-track a quantum leap in the field.

The Chagnon Family and Brain Canada (the “**Partners**”) will fund multidisciplinary teams of health researchers and health professionals that propose original, promising, and transformative interventions in human subjects for primary and secondary prevention of ADRD. Primary prevention refers to reducing the probability that an individual will ever develop an ADRD, and secondary prevention refers to delaying, arresting, or reversing the symptoms of ADRD in affected individuals at the onset of the disease. Funded projects must have the potential to lead to major improvements in addressing the challenges of ADRD through the development of highly innovative preventive strategies.

It is expected that three to five teams will be funded, for five years, in the range of \$1-2M per year per team. There is a possibility that a further five years of funding will be available for studies that require a ten-year timeline, following a second Evaluation Committee review in year five. Projects may be proposed that require larger budgets if the applicants can find supplementary funding partners.

The Partners aim to support potentially high-gain research that might have difficulty being funded by other agencies, perhaps because it is conceptually ahead of its time, involves unusual alliances between disciplines, and features novel approaches, including interventions involving complementary and alternative medicine¹, and alternative uses for existing medications approved for other conditions.

¹ These are defined by the National Center for Complementary and Alternative Medicine as “a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine”. The Center also notes that “The boundaries between CAM and conventional medicine are not absolute, and specific CAM practices may, over time, become widely accepted.”

National Center for Complementary and Alternative Medicine: <http://nccam.nih.gov/health/whatisacam>

The Partners appreciate the effort involved in preparing multidisciplinary team applications, and understand the frustration of low success rates. To encourage imaginative proposals from the widest range of multidisciplinary teams, this application process features a simple letter of intent review that focuses on innovative ideas and the applicants' track record. A limited number of full applications will then be invited, to ensure a high success rate. Following the full application review, three to five teams may be funded.

Scope and Focus

- This competition is exclusively for research dealing with interventions in human subjects, intended to lead to new prevention strategies and preventive treatments for ADRD. Proposals addressing normal brain function, basic disease mechanisms, or animal models of disease are ineligible, as are requests for core facilities, research platforms, technology transfer, or business development activities.
- The competition is open to proposals that will assess the effectiveness of a range of innovative interventions, primarily nutritional or pharmaceutical, individually or combined with behavioural, social, cognitive and activity-based approaches. Reflecting on the lack of success of orthodox approaches, the Partners wish to encourage proposals dealing with novel interventions, including those that are not generally considered part of conventional medicine. Applications should reflect ideas substantially different from mainstream concepts. All proposed interventions must have a sound scientific rationale, including adequate evidence of safety in humans, in order to be considered for funding.
- The Partners are seeking interventions that will primarily focus on a high risk population of asymptomatic individuals and on patients with ADRD at the early onset of their disease, from families with a first or second degree familial history of ADRD disease. However, other cohorts, such as individuals in the early stages of ADRD and with no family history, may be studied if they can be strongly linked to the goals of primary and secondary prevention.
- The proposal must be feasible within the time and budget of these MIRI grants. The team must describe the specific outcome anticipated at the end of the five years of funding, and how, if successful in achieving it, they plan to move the intervention forward into practice, bearing in mind the need for interventions that are affordable for individuals and the health care system. To ensure that research findings have the greatest impact on prevention, the team must provide a plan for dissemination and knowledge translation. The team must commit to making research papers available within six months of publication on open access repositories that will provide free public access to their work.
- The Partners encourage the formation of novel collaborations between clinical scientists, biomedical researchers, academia and industry, including provision of in-kind support by industry. International collaborations are also welcome to further stimulate novel thinking, to access data obtained from cohorts outside Canada, and to disseminate results more widely. MIRI grants can be used to facilitate international collaboration by supporting researcher exchanges and travel between research sites, but can only support work conducted in Canada. International collaborators will supply their own operating funds for the joint project. The Partners may also establish funding partnerships with organizations in other countries to jointly support international research collaborations.

- It is expected that data generated in these projects will be shared with and accessible to other researchers as soon as possible after it is generated, and in a form that respects the privacy of participants, in order to benefit the worldwide effort against ADRD. This open sharing is subject to temporary confidentiality requirements necessary for protection and exploitation of intellectual property (IP).
- The Partners desire that IP originating from work funded by these grants will be developed to maximize the benefits and provide such benefits at reasonable cost to the public.
- The Partners have committed a total of \$25M over five years to this competition, to support several grants of up to \$2,000,000 a year until March 31, 2017 for a maximum of \$10M per grant. Most grants will be less than the maximum. Applicants may provide a rationale for a different annual funding profile if this facilitates their proposed research activities. Applicants may propose a project with a budget greater than this, with the additional funding contributed by a supplementary funding partner that they have recruited, whose contribution may be matched by the Canada Brain Research Fund. Applicants considering this strategy should contact Brain Canada for advice (ADRD_query@braincanada.ca).
- MIRI grants may be used to support any aspect of the operating costs of the research project, including: supplies and materials, provision of special clinical services and user fees, subject recruitment and compensation for out-of-pocket expenses, maintenance of essential equipment, travel of team members and trainees for collaboration and presentation of results, publication costs, salaries for technical and clinical personnel, stipends of trainees, and equipment that is currently unavailable but essential for the project. MIRI grants may not be used: for salary payments to any team members who are eligible to apply for operating grants from the federal granting agencies, payment to clinicians for recruiting subjects, real property costs and lobbying activities. The Partners' grants do not provide institutional overhead.
- These MIRI grants are non-renewable. After five years, successful projects should be at a point where other private or public sector support is available to continue the development of proven interventions. However, the Partners recognize that it may take longer than five years to demonstrate the efficacy of some types of intervention, and there is the possibility of receiving a further five years of support by the Chagnon family and other partners, subject to an Evaluation Committee review of progress to date, and potential for continued and future impact.

Eligibility

This competition is open to teams of two or more investigators, based at Canadian institutions, in any health or health care discipline, who are eligible to apply for research grants from the Canadian federal granting agencies (CIHR, NSERC and SSHRC).

- One of the team members will be chosen by them to be the Team Leader, and will be the individual responsible for communication with the Partners. If the Team Leader is not a health care professional licensed to practice in Canada, a licensed Clinical Team Leader will also be chosen.
- Teams must be multidisciplinary and their members may be based in one or several provinces or research institutions. The Partners encourage collaboration between clinician scientists and biomedical researchers, and the participation of behavioral scientists, psychologists, sociologists, health economists and population health researchers, as appropriate. The team must include the range of expertise and experience required to carry out the proposed intervention.

- The Partners encourage international collaboration and the formation of teams that include researchers at all stages of their careers.
- Collaborators from government, not-for-profit and private sectors and other nations are also welcomed in order to strengthen teams and facilitate the uptake of their findings, but the Partners' funds will only support the portion of the work conducted in Canadian institutions eligible to receive funding from the federal granting agencies.
- It is not necessary to have funding commitments from supplementary funding partners in order to submit a letter of intent.

Criteria for Assessment of the Letter of Intent

- **Impact:** Since this funding initiative is outcome-focused, the essential element in the assessment of these LOIs is confidence that the project will have an impact on prevention of ADRD. The interventional project will generate results that are valid, reliable, applicable to real-life populations, and will serve prevention strategies or preventive treatments. Satisfying the other three criteria increases confidence in this prediction, but ultimately, the project will be judged on its potential for impact.
- **Innovation and originality:** Only proposals of an international calibre of excellence will be funded. These will be proposals that are solidly-based in scientific fact, and which offer promising new approaches to primary and secondary prevention of ADRD in a high-risk population, with evidence of “outside the box” thinking in terms of concept or approach and should reflect ideas substantially different from mainstream concepts. Proposals must not duplicate other currently-funded research projects, but, with adequate justification, they may be complementary to, build on, or extend them. Since a track record of innovative and relevant research, appropriate for career stage, is a predictor of future performance, quality of the team will also be a critical component of the assessment.
- **Feasibility:** The goals of the project are attainable within the time and funding available, and the approach is realistic, ethical, and technically feasible (it is understood that it may take longer than five years to demonstrate the efficacy of some types of intervention, particularly in a population of asymptomatic individuals). The team has a realistic and effective plan for further development of the intervention at the end of the funding period and the LOI describes such plan, including the commercialization or future use potential, if any.
- **Multidisciplinary and teamwork:** Members from different health disciplines contribute a specific value to the team, and the team as a whole achieves synergy of effort in order to achieve goals and accelerate progress.

Sharing of Applications with Partners

Partners and any other funding partners will have access to the full contents of relevant LOIs and applications, under confidentiality agreements. Representatives of funding Partners will be invited to attend reviews of LOIs or full applications.

Applicants are advised to consult the Brain Canada website for details of how the Canada Brain Research Fund and partnerships will operate. A separate section for this initiative will be created.

Timeline

The timeline has been developed to ensure that applicants have sufficient time to prepare their submissions and that the review process be of the highest quality and integrity. Every effort has been made to reach the balance between these objectives and commencing funding as soon as possible.

Call for Applications:	December 19, 2012
Deadline for Receipt of Letters of Intent:	16.00 EST February 22, 2013
Review of Letters of Intent:	March – April 2013
Invitations to Apply sent:	April 29, 2013
Deadline for Receipt of Full Applications:	16.00 EDT July 12, 2013
Review of Full Applications:	July-August, 2013
Notification of Conditional Award sent:	September 16, 2013
Due diligence for removal of conditions:	September-October, 2013
Funding begins:	Earliest date, October 14, 2013

Letter of Intent (LOI)

Team leaders should contact Brain Canada (ADRD_query@braincanada.ca) with enquiries about the LOI process.

Before 16.00 EDST on February 22, 2013, the team leader must send an email with the subject line “ADRD LOI submission” to ADRD_LOI@braincanada.ca, attaching a Portable Document Format (PDF) file containing the following information:

- **Cover Page:**
 - Title of proposal;
 - Name and contact details of team leader;
 - Amount requested in each of 5 years;
 - Up to 10 key words;
 - The following statement: “I certify that all members of the team have agreed to their inclusion in this LOI, and allow me to represent them throughout the application process. I also certify that all team members permit the Partners to circulate this LOI and subsequent full application to other potential partners, under a confidentiality agreement, for the purpose of securing additional funding”;
 - Signature of the team leader, date.
- **Pages 1a, b and c:** A summary of the intervention research project, its endpoints and goals, emphasizing the scientific rationale for the planned intervention, and mentioning supporting studies that justify the application of the intervention to the chosen study population. The summary must address all the evaluation criteria. This section should also contain a self-appraisal of the quality of the proposed intervention study, addressing methodological issues relevant for the type of study

design (three pages).

- **Page 2:** A description of the applicant's plans for data sharing (half a page). A description of the anticipated specific outcomes of the project, and their impact on prevention of ADRD (half a page).
- **Page 3:** An explanation and plan for how the applicants propose to further develop the intervention and apply it to practice after the end of this grant, respecting the principle that any IP originating from the MIRI grant will be developed to maximize the benefit and minimize the cost to the public (half a page).
- **Pages 4a, b, c, etc.:** Provide the name, institution and disciplinary affiliation of each team member, including those from industry, not-for-profit organizations, government and other countries. Explain why each is essential to the project, and end with an overview of how the team will work together (ten lines for each team member, half page for team overview).
- **Pages 5a, b, c, etc.:** For each team member, cite up to five of their recent publications. Publications should provide evidence of innovative thinking and approaches, and for clinician scientists they should also illustrate the member's previous experience in clinical human intervention research in the area of primary or secondary prevention of ADRD, thus providing evidence of the applicant's technical ability to contribute to the proposed intervention project. Publications or collaborations in the research area of complementary or alternative medicine would be an asset. Each item should be annotated with a brief reason for the selection. Include the digital object identifier (DOI), URL, or PubMed identifier (PMID) where applicable so that reviewers can more easily access them (up to one page for each member).
- **Pages 6a, b:** An outline budget for the project, over its total duration, indicating the anticipated in-kind and cash contributions by other funders where appropriate (two pages).
- **Page 7: References** (up to one page).
- **Page 8, voluntary:** Names and contact information for three individuals not in conflict who would be competent to evaluate the LOI and subsequent full application, if invited (up to half a page). The Partners appreciate these suggestions, but do not commit to use them.

Use 12 point Arial or Georgia font, single-spaced, on a letter-size page with 1" minimum margins. It is the sole responsibility of the applicants to ensure their LOI submission is acceptable and received before the deadline. Those received in any other format, exceeding the page limits, incomplete or late, will be rejected. Brain Canada will acknowledge receipt of LOIs by email within one working day.

The Partners do *not* require at the LOI stage signatures denoting institutional support, funding commitments from supplementary partners, regulatory or ethical approval, details of their institutional IP policies, CVs, copies of publications, etc. Material extraneous to that requested above will be removed before the LOI is sent to the reviewers.

Full MIRI Applications

Further details of the process will be provided to those invited to submit full applications. These will be up to **11 pages in length**, including an outline budget, and will be accompanied by a full CV for team members eligible for funding. The criteria for assessment will be essentially the same as for the LOI, but may be modified or weighted on the basis of experience gained during review of the LOIs. Applicants will also provide full details on the steps they will take to: protect the privacy and well-being

of study participants; ensure the objective oversight of the study; guarantee the integrity and security of study data; and protect and develop IP that originates from the funded research while upholding the principle of maximizing the benefits and providing such benefits at reasonable cost to the public.

In the case of proposals to use natural products, applicants will have to provide sufficient information to allow the reviewers to assess the integrity, purity, composition and strength of the natural product. Applicants are referred to the policy of the National Center for Complementary and Alternative Medicine for information that should be included in a grant application (<http://nccam.nih.gov/research/policies/naturalproduct.htm>).

The Partners recognize that because of the rapid pace of discovery in the field of ADRD, there may be changes in the project description or team membership between LOI and full application. Full applications that are judged by the Partners to differ substantially from the LOI will be referred to the Chairs of the LOI and full application Selection Committees. If the Chairs agree that the revisions have made the application more responsive to the assessment criteria it will be accepted. Revisions that are consistent with specific advice from the Partners will of course be acceptable.

Review and Decision Process

Step 1: Review of Letter of Intent. The Partners will appoint an expert Selection Committee to assess all LOIs and subsequent full applications against the review criteria. The Committee will be composed of experts of international stature, who are not applicants, from within and outside Canada. Collectively, the composition of the Committee will reflect the intervention approaches covered by the LOIs received, and will contain individuals expert in the current state of knowledge about the technical aspects of human intervention studies for prevention of ADRD, those involving complementary and alternative approaches, the genetics, etiology and pathophysiology of ADRD, and the ethical aspects of intervention studies involving the elderly and those with cognitive impairment. The Selection Committee will provide a merit score for each LOI and, for those with a sufficiently high score, recommend to the Partners that the team leader be invited to submit a full application.

To ensure a reasonable success rate, the number of applications invited will be two to three times the number that can be funded. Team leaders will receive brief comments from the Selection Committee explaining the reasons for invitation or non-invitation. The project titles and names of members of the teams invited to submit full applications will be published on the Brain Canada website. The Partners may advise teams that have submitted similar or complementary LOIs that they should consider a joint proposal.

Step 2: Review of Full MIRI Applications. Full applications will be reviewed by two Expert Reviewers whose assessments will be provided to the Selection Committee, and each application will also be reviewed by two Selection Committee members. To ensure a fair review and minimize the possibility of misunderstandings, the Selection Committee will schedule a 20-30 minute tele- or video-conference with each team leader, who may be supported by two team members. This permits the Selection Committee to clarify unresolved issues, and the applicants to respond to specific criticism.

The Selection Committee will provide a merit score for each application, and recommend to the Partners, those applications that have received a sufficiently high merit score to be worthy of approval, subject to the availability of matching funds. All applicants will receive written comments from the Selection Committee. The Partners will not entertain appeals against the assessment of the Selection Committee.

The Selection Committee membership will be posted on the Brain Canada website after the

competition.

Step 3: Allocation of funding. Funding will be allocated, first and foremost, on merit. Only excellent applications, as judged by the Selection Committee will be recommended to the Partners for funding. Such excellent applications will be conditionally approved by the Partners in order of merit until funds are exhausted. Successful applicants will be notified that their proposals have been conditionally approved, and informed of the conditions that must be met before funding can be released.

After this initial allocation process there may remain some fundable applications for which Partner funding is not available. Brain Canada will work with the investigators to help secure funds from other eligible partners, within a reasonable time limit.

If application quality does not meet their high standards, the Partners may fund fewer applications than planned, and re-launch the competition.

Step 4: Due diligence. In order to reduce the burden on applicants, Partners require certain documentation (e.g. detailed budgets, details of concurrent research funding, regulatory and ethics approval, institutional IP and commercialization policies) only from those applicants whose MIRI projects have been conditionally approved, though **time-consuming items such as ethics approval should be sought as early as possible by applicants invited to submit a full application.** The required documents must be received and other conditions resolved within a reasonable period specified by the Partners, before funds can be released to the institution of the team leader. The institution of the team leader is responsible for distributing funds to the other team members, through their institutions.

Confidentiality and Ownership

The Partners own all materials submitted for both LOI and full MIRI competitions. They will take reasonable steps to keep these materials confidential, and divulge them only to reviewers, Selection Committee observers, and representatives of the Partners, who have signed confidentiality agreements. Funded applications will be retained for comparison of intended and actual outcomes, as part of the final evaluation of this partnership, and of the Canada Brain Research Fund.

The Partners do not claim ownership of IP arising from research that they fund. To satisfy the expectation that that any IP originating from the MIRI grant will be developed to maximize the benefit and minimize the cost to Canadians, successful applicants will have to provide details of their institutional IP policies for approval before funding can begin. They will also inform the Partners when such IP has been disclosed (declaration of invention), and the Chagnon family will request a seat on the commercialization committee established by the institution. If the owner of the IP decides to abandon its commercialization, the Chagnon family will be offered the right to pursue this commercialization. Full details of this policy will be provided to successful applicants.

Reporting, Communications, and Evaluation

With their emphasis on impact, the Partners require ongoing evaluation of funded projects and the achievement of interim goals on the way to the anticipated outcomes. Detailed reporting requirements will be provided to applicants who are invited to submit a full application. They will include an annual audited financial and a scientific report, and the Partners will also require that they are represented on a data and safety monitoring committee for the intervention study.

The Partners will support truly innovative and therefore risky research. They need to know if these risks are acceptable. As a condition of continued annual funding of MIRIs, the Partners require a biannual progress report from the team leader, outlining project achievements and impacts realised, as well as difficulties encountered and steps taken to overcome them. Progress reports will be reviewed by the Partners and members of the Selection Committee, with continued funding based upon a satisfactory review. If the Partners consider that a progress report is questionable, after discussion with the team, it may provide an extension to the period over which the funds are available, or cancel further funding. Details of the reporting process will be provided to funded MIRIs.

In order to demonstrate to Canadians the ongoing value of the Canada Brain Research Fund, MIRI team members will contact Partners in advance of the publication, release or public presentation of research results obtained with Partners funding, so that a press release or other publicity can be prepared. Embargoes will be strictly respected. Acknowledgment of Partners funding will accompany all publication, release or presentation of such research results.

Funded teams will be required to register their study according to the policy of the International Committee of Medical Journal Editors². They will be asked to publish their results where they will have the greatest visibility. They must make publications arising from work funded by these grants freely available for public access within six months of publication date either through the journal of publication, or by posting a copy of their paper in a standard repository, such as PubMed Central and register with a known clinical trials register such as ClinicalTrials.gov or <http://www.controlled-trials.com/>.

At the end of the current Brain Canada Research Fund, Brain Canada wants to show that exceptional value was received for the investments of the federal government and the other partners. It needs to know the impact of every grant and award. Ten percent of the final year's funding will be withheld by the Partners and released on receipt of a satisfactory end-of-project report that describes the current and estimated future outputs and impacts of the MIRI research project, including dissemination of findings and knowledge translation and exchange.

The Partners may instigate an audit of their financial contribution to the project at any time.

For further Information

About Brain Canada and the Canada Brain Research Fund: <http://braincanada.ca/>

About this MIRI competition: ADRD_query@braincanada.ca

² http://www.icmje.org/faq_clinical.html

Financial contribution from



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About the Canada Brain Research Fund

The Canada Brain Research Fund is a public-private partnership designed to encourage Canadians to increase their support of brain research, and maximize the impact and efficiency of those investments. Brain Canada has committed to raising \$100 million from private donors, which will be matched by government on a 1:1 basis. The Fund was announced in federal budget 2011, which proposed to “allocate up to \$100 million to establish the Canada Brain Research Fund, which will support the very best Canadian neuroscience, fostering collaborative research and accelerating the pace of discovery, in order to improve the health and quality of life of Canadians who suffer from brain disorders.”

The combined investment will fund research in ways that will accelerate the translation of research into new diagnostics, treatments and ultimately cures. Brain Canada will encourage all organizations raising funds for brain research to contribute directly to the fund and have their donor dollars matched, and/or to partner on research programs to further leverage the public-private match. Partnering with the Canadian Association for Neuroscience, Brain Canada has developed a national research program that will support areas of the greatest potential and need. Brain Canada believes that a collaborative approach to research will accelerate the translation of research discoveries into prevention, treatment and cure. Its approach will be to focus on the brain as a single complex system, rather than a collection of distinct diseases. The Multi-Investigator Research Initiative was the first of the Fund’s research programs, followed by Training Awards. Platform Support Grants for development and operating support of national neuroscience research resources will be announced in the coming months.