WESTON BRAIN INSTITUTE

LETTER OF INTENT
Transformational Research: Canada 2019
Alzheimer's & Related Disorders

DEADLINE: **Monday April 1, 2:00pm EST**
Applicants will be notified of Proposal invitations in June 2019.

This Letter of Intent is an example only. Do not complete this paper application.
Please submit the Letter of Intent online through the Institute's grant management system at https://weston.smartsimple.ca/welcome/neuroscience

Application Number:

Principal Applicant:

Project Title:

Applicant Details

	Team Members	Organizations	Primary Contact Information	Role in Project	Estimated Time Spent on Project
1.	Salutation: First Name: Last Name:	Primary Organization: Position Title: Other Affiliations/ Position Titles:	Address: Phone: Email:	☐ Principal Applicant ☐ Co-Applicant ☐ Collaborator	%
2.	Salutation: First Name: Last Name:	Primary Organization: Position Title: Other Affiliations/ Position Titles:	Address: Phone: Email:	☐ Principal Applicant ☐ Co-Applicant ☐ Collaborator	%

Note: Projects are not limited to two team members as laid out on this sample application form; projects may include as many team members as needed for the successful execution of the project.

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Application Overview

1. Keywords to describe the proposed work:

NEW for 2019:

For the Transformational Research: Canada 2019 program no preliminary data is required; instead it can be collected as an initial milestone with well defined, quantifiable go/ no go criteria. The structure of the project and budget should match the quality of the preliminary data.

Expanding the type of complementary approaches eligible for funding to other lifestyle interventions including but not limited to: speech therapy, cognitive therapy, music therapy, social interaction, if these applications meet our other scope criteria and have specific supportive evidence/justification (from published literature or unpublished data) to warrant further investigation.

Encouraging applications that bring in other fields such as: AI, big data, machine learning, data science, and computer science.

The Institute defines neurodegenerative diseases of aging to include:

- Alzheimer's disease
- Dementia with Lewy bodies
- Frontotemporal dementia
- Multiple system atrophy
- Parkinson's disease
- Progressive supranuclear palsy
- Vascular contributions to the above diseases (not stroke-mediated vascular disease)
- Prodromes to the above diseases, including
    - Mild cognitive impairment as prodromal to Alzheimer's disease
    - REM sleep behaviour disorder as prodromal to Parkinson's disease

Proposed projects may relate to any disease(s) but must have impact on the diseases above and will be adjudicated based on their potential impact on these diseases.

The Institute defines translational research to be:

Applied research towards developing therapeutics for the prevention and/or treatment of human disease. For example, for small molecule drug development, this includes target validation to Phase IIa clinical trials. Basic/discovery research, including but not limited to understanding disease mechanisms and discovering genes implicated in disease, is not in scope.

The Institute defines therapeutics to be:

A pharmacological approach (including small molecules, biologics, cell therapies and vaccines, including drug repositioning and repurposing), medical device, surgical intervention, or magnetic or electrical brain stimulation. Therapeutics can be for symptomatic relief, disease modification, or prevention. Complementary

approaches such as, acupuncture, music, and social interaction are not considered therapeutics. Identification of novel therapeutics is in scope (e.g., high throughput compound screens); however, identification of novel targets is out of scope. Identification of therapeutic targets is not in scope, including genes implicated in disease.

The Institute defines tools to be:

Items that accelerates development of therapeutics, e.g., imaging techniques or reagents, biomarkers, and diagnostics.

- Tools must have direct impact on the translational development of therapeutics (as defined by the Institute, i.e., target validation to phase IIa clinical trials) for neurodegenerative diseases of aging and will be valued only on their ability to do this.
    - Any value the tools contribute to basic research will not be taken into consideration. For example, tools will not be valued for their ability to identify new targets or understand disease mechanisms.
- Projects covering only the discovery/identification of a tool are out of scope.

Notes about biomarkers:

- Biomarkers must be being developed for human disease diagnosis, prognosis, for patient stratification to clinical trials or to predict response to therapies (surrogate for a clinical endpoint).
    - Biomarkers should measure pathology of the disease (e.g., fluid, imaging or tissue biopsy derived biomarkers) and not be based on behavioural phenotypes (e.g., gait or grip strength).
    - Genetic biomarkers including somatic mutations, SNPs, epigenetics and gene products are in scope if they meet the other eligibility criteria.

- If the project includes biomarker identification:
    - The project must also include experiments to validate the biomarker.
    - All the samples/data necessary for identification and validation must already be available/collected unless there is sufficient justification to collect new samples/data (e.g., samples cannot be stored).
    - Validation of biomarkers must occur in a well-characterized human subjects/samples/data. This validation must be in samples/data from different subjects than those used to identify the biomarker.
    - Post mortem tissue can only be used for validation of biomarkers previously identified in living subjects.

      An identified biomarker is defined by the Institute as one that meets the following 4 conditions:

- Specific item(s) or signature to be measured can be defined;
    - For e.g.,
        - Presence of a particular bacterium
        - Disease-specific EEG signature
        - Specific brain structure with reduced volume

        - Single protein increased
        - Precisely defined fingerprint
            - If the biomarker is a fingerprint of a family of proteins or a signature of brain volume changes, the precise fingerprint or signature to be replicated must be previously determined. For e.g., omics studies for the purpose of identifying biomarker patterns or signatures are out of scope.
        - Exact identities of multiple individual factors that may be useful individually or as a specific composite
    - It is not in scope to know that a family of proteins is affected or that brain volume is changed overall, if the specific item or signature that is the biomarker cannot yet be specified. For example, a single protein is not considered an identified biomarker if only the family of proteins were previously identified to be affected.
- In what it will be detected (e.g., which tissue/fluid), using what assay, and for what disease, can be clearly stated;
- Specific item(s) (or signature) to be measured has been shown to be detectable in humans or human-derived samples/data in the tissue/fluid to be tested;
- Compelling data exists to justify moving to validation (as defined by the Institute).
    - The most compelling data is likely in humans or human-derived samples/data with a relevant disease
    - The most compelling data will likely allow for a power calculation
    - Data from pathophysiologically relevant animal models could be considered if those animal data are compelling

Biomarker validation is defined by the Institute as:

- Testing a previously identified biomarker in a sufficient number of appropriate, comparable, well-characterized human subjects/samples/data to determine whether it is a sensitive and/or accurate biomarker.
    - If the proposed assay is different than the one used for initial biomarker identification, or if the assay will be used in a different type of specimen (e.g., different tissue/fluid or different species) then preliminary data must be provided to demonstrate that the assay works appropriately. For example, if a biomarker was identified using an assay in CSF and you are proposing to use the same assay to validate a biomarker in blood, there must be preliminary data demonstrating the assay works in blood.
    - Replication studies are not considered to be validation, e.g., using subjects with a different disease stage, or subjects on different drug regime if that regime could affect the biomarker.

For cognitive assessment tools and clinical assessment instruments:

- If developing a cognitive assessment tool or a clinical assessment instrument, the tool must be evaluated on patients with a relevant disease.
    - E.g., development of a questionnaire to assess cognitive decline.
- Requires discussion of why the new assessment would be better than existing ones

- **Clinical trial:** Research in which one or more human subjects are prospectively assigned to one or

more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

- **Clinical trial sub-study:** A study investigating a question not addressed by the main trial and which may involve obtaining additional measurements and data collection from a sub-group of all participants from the main trial.

Notes about complementary approaches
Expanding complementary approaches section to also include other lifestyle interventions.

Accepting applications on complementary approaches and lifestyle interventions if these applications meet our other scope criteria as listed below.

Based on the success of the of the 2018 pilot allowing interventions of diet, physical activity, sleep and nutritional supplements, other kinds of "complementary" or "lifestyle" interventions are now eligible. This includes but is not limited to speech therapy, cognitive therapy, music therapy, and social interaction. Projects are eligible for funding through the Rapid Response, Transformational Research, Early Phase Clinical Trials programs and Big Ideas programs. Applications on these topics are eligible if they meet our disease and project scope criteria above and the following criteria:

- Includes specific supportive evidence/rationale (published literature or unpublished data) to justify further investigation.
- Similar experimental design is used to test the approach as would be implemented to test therapeutics, including appropriate control groups.
    - Any interventional trials should address, as best as possible, the potential confound of placebo effect.
- Measures outcomes relevant to neurodegenerative diseases of aging (as defined by the Institute).
- Interventions are being investigated in relevant human cohorts and/or appropriate disease models (e.g., cell culture, *in silico*, or animals).
- Has direct impact on accelerating the development of treatments for neurodegenerative diseases of aging. Treatments can be for disease modification, symptomatic relief, or prevention.

Examples of projects that are considered out of scope for this program call, but could be considered in scope for future programs:

- An exercise intervention aimed at reducing obesity, blood pressure and resting heart rate in subjects with subjective cognitive impairment.
- Testing whether a 12-month paleo diet intervention improves cognition in healthy older subjects.

Examples of projects that are considered in scope:

- *In silico* screen of a library of nutritional supplements to select those that reduce amyloid plaques.
- Testing whether a 12-month paleo diet intervention improves MoCA scores or amyloid deposition in subjects with mild to moderate AD.

If you are interested in applying with a project that incorporates complementary approaches and/or lifestyle interventions, you are encouraged to contact Matthew Sacheli (+1-416-967-7828, matthew.sacheli@westonbrain.org) to discuss whether your project is in scope.

2. What type of tool, therapeutic or complementary approach is being developed as the primary goal of the project?

*(Please select only one - tool or therapeutic – that is being **developed** as the primary goal of the project, e.g., do not select "Animal model" unless you are developing a new animal model.)*

Tool
- ☐ Animal model
- ☐ Assay/screen
- ☐ Biomarker
- ☐ Cell line
- ☐ Clinical assessment instruments
- ☐ Diagnostic
- ☐ Imaging technique or reagent
- ☐ New method of drug delivery
- ☐ Probe
- ☐ Other *Please specify:*

Therapeutic
- ☐ Biologic
- ☐ Cell therapy
- ☐ Electrical brain stimulation
- ☐ Magnetic brain stimulation
- ☐ Medical device
- ☐ Small molecule
- ☐ Surgical intervention
- ☐ Vaccine
- ☐ Other *Please specify:*

Complementary approaches
- ☐ Sleep intervention
- ☐ Exercise intervention
- ☐ Diet intervention
- ☐ Nutritional supplement
- ☐ Other complimentary approaches

If you selected 'biomarker' above, what is the primary purpose of the biomarker?
- ☐ Diagnostic – determine whether patients have a particular disease or disease subset
- ☐ Prognostic – indicate future clinical progression
- ☐ Predictive, for patient stratification to clinical trials – identify patients likely to respond (favourably or unfavourably) to a specific treatment
- ☐ Response to therapy – indicate that the biological response to a therapeutic intervention is associated with clinical benefit (i.e., surrogate for a clinical end point)

3. If a tool is being developed, please specify the type of tool being proposed in the project. If the proposed tool is a biomarker, please provide one sentence to answer the following question, being as specific as possible: What biomarker in what tissue/fluid/location are you measuring, using what technique, for what purpose, in which disease? If you are not developing a tool, please type "None".

4. If a therapeutic is being developed as the primary goal of the project, what preclinical phase(s) of development does the project cover?

(Select only those that apply.)

- ☐ Target validation
- ☐ Assay development
- ☐ Screening and hits to leads
- ☐ Lead optimization
- ☐ Safety and toxicity in animals
- ☐ Efficacy in animals
- ☐ None
- ☐ Other *Please specify:*

5. Research will have a significant impact in which neurodegenerative disease(s) of aging?
(Select only those that apply. There is no benefit to selecting more diseases.)

☐ Alzheimer's disease
☐ Dementia with Lewy bodies
☐ Frontotemporal dementia
☐ Multiple system atrophy
☐ Parkinson's disease
☐ Progressive supranuclear palsy
☐ Vascular contributions to the listed diseases (not stroke-mediated vascular disease)
☐ Prodromes to the listed diseases (please also check the disease(s) to which your condition is a prodrome)

6. Relevance of proposed work to the Institute's mandate: using the Institute's definitions (above), explain how the primary tool or therapeutic being developed in this project (as identified in question 2 above) is translational research, and will accelerate the development of therapeutics for neurodegenerative diseases of aging. For tools, this requires addressing how the tool will have immediate impact on accelerating translational research on therapeutics*. (maximum 200 words.)*

7. What type of tool(s) and/or therapeutic(s) and/or complementary approach(es) is being developed aside from the primary goal of the project?
(E.g., do not select "Animal model" unless you are developing a new animal model. There is no benefit to selecting more items than fewer items. Select "None" if there are no tool(s) and/or therapeutic(s) being developed aside from the primary goal of the project.)

Tool
☐ Animal model
☐ Assay/screen
☐ Biomarker
☐ Cell line
☐ Clinical assessment instruments
☐ Diagnostic
☐ Imaging technique or reagent
☐ New method of drug delivery
☐ Probe
☐ Other *Please specify:*

Therapeutic
☐ Biologic
☐ Cell therapy
☐ Electrical brain stimulation
☐ Magnetic brain stimulation
☐ Medical device
☐ Small molecule
☐ Surgical intervention
☐ Vaccine
☐ Other *Please specify:*

Complementary approaches
☐ Sleep intervention
☐ Exercise intervention
☐ Diet intervention
☐ Nutritional supplement
☐ Other complimentary approaches

☐ None

If you selected 'biomarker' above, what is the primary purpose of the biomarker?
- ☐ Diagnostic – determine whether patients have a particular disease or disease subset
- ☐ Prognostic – indicate future clinical progression
- ☐ Predictive, for patient stratification to clinical trials – identify patients likely to respond (favourably or unfavourably) to a specific treatment
- ☐ Response to therapy – indicate that the biological response to a therapeutic intervention is associated with clinical benefit (i.e., surrogate for a clinical end point)

Please provide one sentence to answer the following question, being as specific as possible. What biomarker in what tissue/fluid/location are you measuring, using what technique, for what purpose, in which disease?

8. Have you applied to the Weston Brain Institute previously with similar proposed work? If so, specify the previous LOI title and program applied to. Please briefly explain how this LOI is different than the previously submitted work. (This information will not be used to assess the application.)	☐ Yes *Please specify:* ☐ No
9. Have you applied to other funding agencies with the same proposed work? *(This information will not be used to assess the application.)*	☐ Yes *Please specify:* ☐ No
10. Is this your first time applying for a neuroscience grant from the Weston Brain Institute? *(This information will not be used to assess the application.)*	☐ Yes ☐ No
11. Is this your first application for a research grant specifically in the area of neurodegenerative diseases of aging? *(This information will not be used to assess the application.)*	☐ Yes ☐ No

The adjudication committee for this program does not include Canadians. Please list the full names of any individuals located outside of Canada who are competitive with you and therefore should not review your application. Please do not exclude reviewers for other reasons as we are unable to honour those requests. Type "None" if you have no reviewer exclusion.

(This information will not be used to assess the application.)

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Project Information

1. Central hypothesis, goals and specific aims: *(maximum 500 words)*

2. Significance and impact: Why is it important that the proposed work be carried out? How will successful completion of this work accelerate the development of therapeutics for neurodegenerative diseases of aging? *(maximum 200 words)*

3. Experimental approach: Please outline how the proposed work will be carried out and interpreted, including clear go/no-go criteria. Please do not include background information (e.g., pathology, etiology or incidence/prevalence) of neurodegenerative diseases of aging. *(maximum 1300 words)*

4. Preliminary/supporting data: A maximum of 1 page of preliminary data that best supports the application can be uploaded as a PDF file, e.g., figures or tables. Note, preliminary/supporting data is not required. If no preliminary data is provided at the time of submission, it is required that preliminary data be obtained as the first critical go/no-go decision point early on during the course of the proposed project.

List of publications cited in the application: Please include full citations with a complete author list and PMID.