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Objective

The objective of this document is to assist researchers in preparing research proposals that are scientifically compelling and easy for reviewers to read. These guidelines may be particularly useful to **applicants**, and may aid **internal reviewers** and grant application **editors**.

Included are proposal-writing ideas and tips from experienced investigators and review panel members, plus tips and examples for writing style and document design.

What do reviewers need to know?

What you or the team plan to do

- Objectives
- Hypotheses or research questions

Why doing this research is important

- New knowledge
- Impact for e.g., society or health

Why doing this research is reasonable

- Review of directly relevant previous work
- Rationale for this research, based on current knowledge
- Preliminary data

How you or the team will do this research

- Work plan
- Details of methods
- Analysis and interpretation of results
- Pitfalls and alternative methods
- Timelines

Why you or the team are the best people to do this research

- Experience and skills
- Collaborators with complementary skills
- Roles of each investigator
- Facilities and infrastructure available to investigators (especially for new investigators or those relying on specialized techniques)

The suggestions that follow will help organize the information needed by reviewers into a coherent and logical proposal, one that scientific reviewers who are not experts in your field can easily read and understand.

Write a proposal that is an 'easy read'

Too many grant proposals remain unfunded, not because they contain poor ideas for research projects, but because the proposals are ineffectively written and thus are scored slightly lower than their well written and easy to read competition.

Define your reviewers

Along with your other thinking before writing a grant proposal, take time for a key mental exercise: define the characteristics of the people who will review the proposal for funding decisions. A clear definition of your reviewers provides a benchmark for the content and style of a proposal. Some simple strategies to define reviewer characteristics as specifically as possible are to:

- talk with individuals similar to your reviewers and readers e.g., colleagues who are not experts in your area of research
- check the characteristics of reviewers who sat on the relevant grant review panel in previous competitions e.g., range of disciplines and expertise, anticipated knowledge of methods and familiarity with the relevant literature
- analyze successful grant proposals from similar competitions for writing style e.g., word choice (formal, technical), length of sentences, variety of sentence types, length of paragraphs

Write for your reviewers

Each funding competition and funding agency has different priorities. Consequently, each grant proposal should be written with those priorities as the guiding principles for proposal style and content. Include an explicit statement of the links between funder priorities and your proposed research.

Reviewers need a document that is **easy and interesting to read**, and **easy to summarize**. Information should be organized with a logical flow that is clear to a reviewer in a related field, but who is not an expert in your field. At the same time the proposal must contain all the details an expert in your field would anticipate. A clear narrative in the proposal, with a beginning, a middle, and an end, helps reviewers to understand your logic. Logical flow can be assessed by a colleague outside your area of research or by a scientific editor.

Reviewers appreciate writing that generates **excitement** and engages the reader. Try using some exciting unusual words to replace standard dry scientific language e.g., 'pivotal' or 'crucial' instead of 'important'. Over-use of unusual words can be tiring for readers, however, so depending heavily on novel language may be counter-productive. Heavy use of technical **jargon** and abbreviations or acronyms also tires reviewers. The target in using unusual or technical language is to spice the proposal lightly, not to smother it with rich sauces.

Positive and definite phrasing impresses reviewers more than tentative and uncertain phrasing e.g., *"We will collect data from participants in July and August, if we are able to enroll sufficient numbers of participants by then…"* versus *"We will collect data from participants in July and August. Our strategies to ensure enrollment of sufficient numbers of participants are …".* Be as positive as you can while remaining honest.

The first page of the proposal is crucial

The first page of the proposal gives the reviewer a road map for this application. A figure illustrating the context and connections of the research aims complements the written material. **A strong first page contains:**

- a short, informative, striking opening sentence that gives immediate context
- the general objective of the research program
- a statement of why the research is important
- a simple, short description of the relevance of the research to e.g., health or disease
- a simple, short description of how the proposed research fits with your previous work
- the overall goal of the grant application, the hypotheses or research questions, and how the hypotheses will be approached
- a brief outline of specific experimental aims and methods
- a summary statement that emphasizes the expected outcomes and the broader importance of the research, to remind the reader of the bigger picture

Within each topic on the first page, guide the reviewer from general to specific points. Aim to convince the reviewer that these research questions are logically the **best possible questions** to ask in this field at this time. Reviewers value a clear answer to the question of "Why should we care about whether this research is done?" Provide information on both what is known and what is not known, demonstrating an understanding of the relevant literature in the field. At the end of each topic, help the reviewer retain the big picture by relating details back to the overall objective or research questions.

Reviewers appreciate a footnote on the first page (small font size) that defines all acronyms and abbreviations used in the proposal.

Strategies for a strong first page can be seen in action in the following **two samples** of first pages from successful proposals.

I. OVERALL OBJECTIVES

Protein folding is a pivotal biological process in both health and disease. **The objective of our research program is to study, at the molecular level, events associated with endoplasmic reticulum (ER)‡ chaperone-dependent protein folding and pathologies.** Understanding these vital processes such as protein folding and ability to modulate Ca homeostasis is important, because many severe diseases including cystic fibrosis, diabetes and neurodegenerative pathologies result from impaired function of the ER membrane.[1-11] Calnexin (CNX) is an ER localized protein important in protein folding and Ca homeostasis. Recently, we created CNX-deficient mice and discovered that they develop neuropathy because of severe problems with myelination. This phenotype is reminiscent of human myelin neuropathies.[12-18] The objectives of the present research project are to build on this discovery. **Therefore, the research outlined in this proposal is centered on the role of CNX and ER proteins in protein folding and quality control in the ER secretory pathway.** We propose to establish the role of CNX and ER quality control, in neuronal pathologies of myelin formation, in protein folding diseases and regulation of ER functions.

II. RATIONALE AND HYPOTHESIS

Why is it critical to study the structure and function of ER chaperones and their role in protein folding diseases? Genetic studies have identified over 16,000 missense mutations leading to single amino acid changes in protein sequences that are linked to human diseases. The majority of these mutations affect protein folding or trafficking, and many disease-linked mutations leading to neuropathies occur in integral membrane proteins, a class of proteins about whose folding we know very little.[12-18] The role of the ER in the biology of myelin integral membrane glycoproteins has not been elucidated. *Why is it important to focus on CNX and other ER quality control components?* Folding of numerous secreted and membrane associated proteins rely on CNX, calreticulin (CRT) and ERp57, components of the ER quality control pathway.[11] We discovered that myelination requires CNX, indicating that CNX may play a role in myelin diseases. *How does CNX affect myelination?* Altered expression of CNX may disrupt folding and functions of peripheral myelin protein zero (P0) and peripheral myelin protein-22 (PMP22). This leads to dysmyelination represented by defective structure and function of myelin in the absence of CNX. *Why is it important to study the role of CRT and ERp57?* CRT is an ER luminal Ca binding homologue of CNX involved in protein folding and regulation of intracellular Ca homeostasis.[4] ERp57 (an ER resident protein disulfide isomerase [PDI]-like protein) is a component of the CRT/CNX cycle involved in formation and isomerization of disulfide bonds in newly synthesized glycoproteins.[19] Studies with CRT and CNX gene knockout mice and CRT- and CNX-deficient cell lines indicate that CRT cannot compensate for the loss of CNX.[20-22] These observations indicate that CRT and CNX are distinct chaperones with unique functions. **Our hypothesis is that CNX is a multifunctional protein which plays a central role in protein folding in the ER and that CNX is critical for embryonic and postnatal development, physiology and congenital diseases.** To test this hypothesis we will address the following questions: *What are the unique molecular elements critical for the chaperone function of CNX? What are the molecular mechanisms responsible for CNX-dependent modulation of folding of myelin proteins and consequently myelination? How do ER quality control components (CRT, CNX, ERp57) impact the folding and trafficking of myelin proteins? How are their contributions interconnected, and how do they intersect with the myelination and protein folding pathways?* We will identify molecular events associated with ER chaperone deficiency during postnatal development and the role of these proteins in myelin formation. We will carry out these studies at several levels of complexity: in gene knockout mice, in protein deficient cells lines, and with purified proteins.

‡**Abbreviations :** ANS, 1-anilino-8-napthalene sulphonate; CD, circular dichroism; CRT, calreticulin; CNX, calnexin; CMT, Charcot-Marie-Tooth; CNS, central nervous system; EndoH; Endoglycosidase F EndoF, N-Glycosidase F; ER, endoplasmic reticulum; IP, immunoprecipitation; MAG, myelin-associated glycoprotein; MOG, myelin oligodendrocytes glycoprotein; MS, mass spectrometry; PDI, protein disulphide isomerase; PLP, proteolipid protein; PNS, peripheral nervous system; PMP22, peripheral myelin protein-22; P0, peripheral myelin protein zero; RT, reverse transcriptase; TAP, tandem affinity purification; TM, transmembrane; UPR, unfolded protein response.

1. INTRODUCTION

Autism is the most severe form of a spectrum of related neurodevelopmental disorders (hereafter, autistic spectrum disorders or ASD) characterized by impairments in socialization and communication and by the presence of repetitive, inflexible behavior. Epidemiologic data indicate that about 1 child in 165 is affected with ASD. Prognosis has historically been poor, with most individuals requiring care throughout their lives, but recent evidence points to much better outcomes with early interventions. The frequency, burden of suffering and efficacy of early intervention for ASD argue for concerted efforts directed at minimizing disability and enhancing outcomes for the many individuals affected by ASD.

Our team's purpose is to describe and examine the interrelationships among early developmental trajectories in children with ASD, to identify specific profiles that can inform earlier diagnosis, and predict later variation in functioning and well-being. Whereas other longitudinal studies of ASD begin after a diagnosis is given, our prospective study of high-risk infants (each with an older sibling with ASD) provides a unique window into earlier processes underlying ASD. Our current CIHR-funded study includes 400 high-risk infants, to our knowledge the largest sample of its kind in the world and one that positions us as international leaders. This study has generated important findings regarding ASD symptoms in the first 18 months, and new insights about patterns of onset and the wider range of features associated with familial liability to ASD and the 'broader autism phenotype'. One particularly intriguing finding is the lack of sex differences in rates and cognitive levels associated with ASD early in life, in contrast to virtually every other study conducted over the past 40 years with older samples. Combined with our unexpectedly high recurrence rate, the lack of sex differences raises interesting questions about whether boys and girls with ASD have divergent trajectories after age 3, with some girls no longer meeting strict DSM-IV criteria for ASD as they get older. We have also delineated unique infant temperament profiles of behavioral reactivity and self-regulation that not only distinguish children with ASD and high-risk infants (regardless of diagnosis) from low risk infants but also correlate with subsequent emotional and behavioral symptoms. These profiles may increase risk of later psychopathology, an area of increasing importance in the field.

In the next phase of this research, we propose to follow this unique cohort to age 8 years, to examine the stability of early ASD diagnoses, to further delineate sex differences in ASD that may emerge over the course of development, and to identify predictors of emotional and behavioral outcomes across the entire high-risk cohort. Longitudinal data already obtained in the first 3 years of life will provide a rich developmental context from which to understand variation in ASD symptoms, emotional and behavioral comorbidities, and overall functioning later in childhood. Indeed, the availability of pre-diagnostic data provides, for the first time, an opportunity to test specific hypotheses about developmental mechanisms underlying key facets of the ASD phenotype, thereby identifying earlier targets for intervention.

2. OBJECTIVES

Within a large cohort of siblings at high risk for ASD, our main objectives are to:

1. Describe the variation in ASD symptom trajectories from infancy to age 8, with special reference to the stability of early ASD diagnoses and the identification of factors (e.g., sex, and early symptom, cognitive and language trajectories) associated with diagnostic instability;
2. Describe the variation in emotional / behavioral trajectories from age 3 to 8, and identify factors (e.g., sex, and early temperament; cognitive and language trajectories; family history of psychopathology) that predict risk of emotional / behavioral disorders by age 8, in both siblings with and without ASD;
3. Compare developmental trajectories of cognitive, language, and adaptive function in boys and girls in the high-risk cohort, to gain further insights into potential sex differences both among those children diagnosed with ASD by age 3, also among their non-ASD-diagnosed sibling counterparts.

Introductory material frames the proposed research

Use the first few pages of the proposal (25 to 30% of total length) to establish the context and foundation for the reviewer.

Significance and relevance to the granting agency objectives

A careful reading of evaluation criteria for the particular grant competition will yield useful information on the objectives of the granting agency. Reviewers are rarely experts in your specific area of research, so the significance and relevance of the proposed work must be stated clearly for a scientific reviewer who is not an expert in the field. Beyond addressing significance and relevance, you can aid reviewers by clearly outlining the uniqueness and potential impact of proposed research.

Background

Most importantly, evaluate each piece of information in the background material. Does the reviewer need to know this? Does it build the case for asking this particular research question? If yes, is this the best place to provide the information? The role of this section is to reinforce the message from the first page: the research questions in this proposal are the best possible questions to ask at this time in this field. **Strong background material:**

- centres on the research question
- develops an argument
- gets to the point reasonably quickly
- integrates previous work by the applicant, placing it in context with examples
- contains key references
- covers multidisciplinary literature
- covers opposing viewpoints in the field, if applicable
- convinces the reviewer that you thoroughly understand the research area

Background material moves from general to specific, so that the research questions are the logical outcome of the background presented.

'Momentum'

The reviewer needs to know how the proposed research builds on your previous work. Previous work does not have to be directly related to this proposal. As part of signalling credibility and feasibility, though, you can describe experience in similar research or methods.

Hypotheses or research questions

The research questions (one or two sentences) are usually stated first in a Summary of Research, and are repeated in the research proposal. Research questions or hypotheses follow background material because the background material logically leads the reader to these specific questions. **A strong research question is**:

- clear and well-stated
- testable

- precisely specified, to justify study design and articulate proposed analyses
- focused on mechanism i.e., not overly descriptive

The number and breadth of research questions in the proposal depends most heavily on career stage. As a general principle, describing a few aims well is more likely to impress reviewers than describing several aims poorly.

A relatively junior investigator. Focus the proposal tightly, with one or two hypotheses or research questions. "Less is more" often applies to applications from junior investigators. Relatively few applications are down-rated for being too modest in their objectives. In contrast, junior investigators often propose far too much, with the result that reviewers request a more focused and feasible re-submission.

A mid-career to senior investigator. Limit the proposal to a few hypotheses or research questions, under the umbrella of a project that is your best research initiative.

Citing the literature

Including citations to both classic and recent papers demonstrates to reviewers that you are fully aware of related research. Don't hesitate to include literature that presents different or contrary points of view. Addressing those differences shows reviewers that you take a thoughtful and well-balanced view of the field. Your proposed research may also aim to resolve those differences. Highlighting controversies in the literature is a particularly effective way to make the case for more research.

Citing relevant papers of your own is one way to exemplify your momentum and expertise in the field. Citing your own work is most important in background material, in preliminary data, and in experimental details. To distinguish citations to your papers, those citations may be highlighted by asterisks, or by citation numbers in bold font. The same style of highlighting may be used for your papers in the reference list.

Preliminary data

High-quality convincing preliminary data are essential to grant applications. Preliminary data are particularly important for new investigators or for new directions being pursued by established investigators. A lack of preliminary data may call into question the validity of the hypothesis, your ability to perform the work, or your ability to interpret the results. Preliminary data support the hypothesis, and require solid substantiation in accompanying figures and tables.

Preliminary data may be included either with introductory material or with relevant sections under experimental methods. The latter suits highly technical preliminary data, which the reviewer may understand more easily in the context of proposed experiments.

Methods and experimental details are the core of the proposal

A suggested allocation of space in a proposal is 1/3 background, 1/3 methods, 1/3 analysis, to demonstrate that you have thoroughly considered all facets of the proposed research. Methods and analyses may be combined under each specific experimental aim or sub-aim.

A **strong presentation of methods**:

- describes the essential features of methods within the research proposal, not in an appendix or a cited publication
- demonstrates that methods are appropriate to the hypothesis or research question
- includes appropriate controls
- includes analyses that map onto the hypothesis and are well-integrated into the proposal

The same research goals may often be reached by different approaches and methods, so discussing and carefully justifying your choice of methods is essential.

Warning: Linear aims

A grant proposal is 'linear' if one experimental aim must succeed before other aims can be carried out. If at all possible, design proposed research to avoid linearity. If the proposal contains any hint of linearity, reviewers will expect inclusion of alternative experimental strategies to work around a possible failure of the first experimental aim.

Pitfalls & potential problems

Recognizing potential pitfalls and problems with experimental approaches is another positive signal to reviewers, indicating that you have carefully thought through all aspects of the proposed research. Discussing implications of potential experimental problems and strategies to deal with them bolsters feasibility. Some proposals may require discussion of logistical challenges e.g., management of multisite studies, implementation of new technology, recruitment/retention of study participants.

Resources

Reviewers need convincing that all the right resources are in place to complete the work as described. These include physical resources such as equipment, space, and access to shared facilities. Intellectual resources are important, too, such as access to databases, prior related work by you, involvement of appropriate collaborators, and skills of experienced research personnel. For new investigators continuing previous post-doctoral research, access to materials such as cell lines or mouse strains may be an essential resource. A letter from the past supervisor can clarify the current relationship with a new investigator.

Timeline

Including a timeline for the proposed work is a tangible demonstration that your thinking is concrete and realistic. Timeline information may be included with individual aims or experiments, or as a separate section of the research proposal. A timeline chart or diagram assists reviewers in understanding projects with multiple stages or complex aims.

Ethics

Ethics approval may not be required at the time of application, but a discussion of any potential problems with ethics may forestall reviewer requests for a more detailed re-submission. Having ethics approval in place before submitting an application avoids these potential reviewer concerns, and demonstrates that you have carefully thought through the ethical implications of the proposed research. Review committees are generally instructed to keep consideration of ethics separate from the final proposal rating. However, an application may be down-rated if reviewers raise flags on major ethics problems. Address ethical implications of data access, confidentiality, and privacy, in addition to any aspects specific to the field or proposed methods.

Teams bring together complementary expertise

One essential component of all grant proposals is convincing reviewers that the applicants plus collaborators have all the necessary expertise to carry out the work. Information on a team of researchers may be included in introductory material, or with relevant aims and experiments, or with summary material near the end of the research proposal.

Assembling the optimal team for a proposal is like fitting together pieces of a jigsaw puzzle, matching shapes, colours, sizes, border or interior piece, sky or ground. A strong team contains members with:

- the mix of expertise that demonstrates feasibility for all aspects of the proposed research
- perspectives from multiple disciplines
- clearly defined roles in the execution of the project
- a mix of experience levels; senior investigators are often *perceived* as contributing a solid track record and demonstrated expertise, while junior investigators are *perceived* as providing enthusiasm and fresh ideas.

Roles of collaborators need to be specified as distinctly as roles of co-applicants. Each collaborator provides a letter of collaboration, if allowed by the funding competition rules (attached in an appendix). Referring to the letters of collaboration in the proposal reinforces for reviewers how each collaborator contributes.

New investigators, in particular, must take care that collaborators do not play too large a role in the proposed research. The applicant should be able to perform the majority of the research independently.

New investigators must take special care if the supervisor from a post-doctoral fellowship is listed as a collaborator. The letter of collaboration from the supervisor should provide a clear statement of the ways in which this research is your independent work.

A final summary brings reviewers back to the big picture

A short summary section at the end of the proposal (1/2 page or less) is an opportunity to emphasize key aspects of the proposal for reviewers. Strategies for a strong end-of-proposal summary are to:

- connect details of experiments back to the hypothesis or research question
- connect specific aims back to significance and impact of proposed research e.g., health burden, treatment options, or other relevant and concrete outcomes
- discuss future plans or research options for the longer term
- discuss how proposed research fits into the long-term development of the field

Dissemination or translation of results may be a necessary research project component. This final summary section can incorporate the knowledge dissemination or translation plan. Integrated and end-of project dissemination strategies are increasingly required by funding agencies, even in basic research proposals, thus an **innovative and practical knowledge translation plan** can provide an extra boost to reviewer ratings.

Pitfalls: Avoid citing future plans that are essentially a collection of loose ends from the proposed work. Also avoid repeating exactly the same summary material that appears in the Summary of Proposal and the first page of the proposal.

Appendix 1. Design and format considerations

A few critical document design features will make your proposal reviewer-friendly, and these features are easy to choose and implement. Although design choices that increase readability may occupy a bit more space, they are worth incorporating into your proposal for the comfort of the reviewer. If proposal material bursts through page limits after you apply good design principles, a colleague or editor can almost certainly trim some extraneous words to bring the proposal back into allowed space.

Design and format help reviewers understand the proposal

- **Headings and subheadings** will guide the reader to each topic and keep them oriented in their mental road map of the application. Headings also aid skimming for key points.
- Using **multiple shorter paragraphs**, with only one idea per paragraph, assists the reviewer in understanding the logic of the proposal.
- '**White space**' is the space around and between document elements. It is essential in any document, helping to visually indicate document organization i.e., which items belong together (words on a line, sentences in a paragraph, etc.) and which are separate. Leaving a reasonable amount of white space makes a document much easier to read. White space belongs in margins, between lines of text, between headings and their paragraphs, between paragraphs, between elements in lists, etc.
- Reviewers appreciate charts, diagrams, flowcharts, etc., that **illustrate key ideas**, preliminary results, and experimental approaches. Moderation is key here, though, both in the number and the complexity of illustrations included in the proposal. As with all material, assess each illustration thoughtfully as to whether it contributes an essential point to the logic of the proposal. Assess the quality of each illustration, also. Poorly reproduced, overly small, or sloppy figures are not helpful to the cause.

Technical points in document design provide easy reading

- Readability of text material is improved when a **serif font** (e.g., Times New Roman) is used. Sans serif fonts (e.g. Calibri) may be used effectively for headings, if desired. Some serif fonts that are efficient for space and easy to read are Times, Times New Roman, and Garamond. Some examples of 12 pt serif fonts are:

  Abcd Efgh *Ijklmn* **Opqrst** 12345^{678} (Times New Roman)

  Abcd Efgh *Ijklmn* **Opqrst** 12345^{678} (Constantia)

  Abcd Efgh *Ijklmn* **Opqrst** 12345^{678} (Garamond)

  Abcd Efgh *Ijklmn* **Opqrst** 12345^{678} (Goudy Old Style)

  Abcd Efgh *Ijklmn* **Opqrst** 12345^{678} (Cambria)

  Abcd Efgh *Ijklmn* **Opqrst** 12345^{678} (Georgia)

  Abcd Efgh *Ijklmn* **Opqrst** 12345^{678} (Palatino)

- Readability of text material declines sharply when **line spacing** is less than single-spaced. Note that spacing less than single-spaced often results in cutting off tops or

tails of long letters such as g and y, giving the impression of a malfunctioning printer. Text set at less than singled-spaced is overly dense and difficult to read.

- Paragraphs may be separated by either a first-line indent or a space between paragraphs. Either technique gives visual white space to distinguish the end of one paragraph and the start of the next. Using both a first-line indent and a space between paragraphs is not necessary for readability, and can take up valuable space for words.

Highlighting key points within text helps a reviewer to navigate and skim

Highlighting of small sections of text is a useful technique to draw the reviewer's eye to key points within a paragraph e.g., objectives, aims, names of techniques in methods. Highlighting is to be used with restraint; too much bold text, for example, gives the impression that the writer is shouting at the reader. Preferred methods to highlight key points are **Bold,** *Italic,* or a font change.

- **Bold** is most useful to **emphasize** a sentence or **parts of a sentence** within a paragraph**.**
- *Italic may be used for a short phrase or sentence, but is tiring to read for longer segments.*
- A font change may be useful for headings e.g., a sans serif font for the heading and a serif font for the associated text.
- Underlining is no longer a recommended method for emphasis within a paragraph; it interferes with any parts of the text below the line, such as subscripts, and looks old-fashioned.

Two sample sets of headings

1)

AIMS AND EXPERIMENTAL DETAILS

(heading for major sections: separate line, border underneath (not underlined), space before and/or after)

Aim 1. Determine the cellular localization of protein X.
(heading for minor sections: separate line, no space after, some form of emphasis e.g., bolding, small caps)

PRELIMINARY DATA. In previous studies, we determined that protein X is membrane-bound...
(heading for sub-sections: heading in line with paragraph, minor emphasis).

2)

AIMS AND EXPERIMENTAL DETAILS

(heading for major sections: separate line, centred, space before and/or after, sans serif font)

AIM 1. Determine the cellular localization of protein X.

(heading for minor sections: separate line, no space after, sans serif font, some form of emphasis e.g., bolding, small caps)

Preliminary data. In previous studies, we determined that protein X is membrane-bound...

(heading for sub-sections: heading in line with paragraph, minor emphasis e.g. italic, sans serif font).