**Template guidelines:** For your grant application, the SERCC strongly recommends using the words that are underlined below as well as retaining the formatting (e.g., underline or bold). The remaining bullet points are provided as suggestions. Instructions from the NIH SF424 are in blue text with additional SERCC comments in gray text.

**Research Training Project Specific Aims**

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| Opening sentence: *A sentence to immediately capture the reviewers’ attention and highlight an area relevant to the targeted program/funding agency.*  Why  Current knowledge: *Information about what is known that will allow reviewers to understand the importance of the proposed research. Sets up the gap/unmet need.*  Knowledge gap or statement of need: *The subject of the proposal; must relate to the previous statements as a next step to advance the field. (Note: it is not essential to use the term “knowledge gap” in this sentence.)*  Consequence(s) of not addressing knowledge gap or need: *Explain why failing to address this gap/need will prevent vertical advancement of the field.* |

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| Long-term goal: *Your long-term career/scientific goal. Should be something that the proposed training plan/research plan will help you attain.* **[NOT necessary to include if this can’t be stated succinctly, but can give reviewers a sense that you are thinking about the value of the award]**   * “My *long-term goal* is to…”   What  Overall objective: *What will be accomplished through this project; must link back to the gap/need you are addressing.*   * “The *overall objective* of the proposed research is to…”   Central Hypothesis: *What must be tested to attain the objective. This should be broad; details will be provided in specific aims.*   * “My *central hypothesis* is that…”   Data to support hypothesis: *Your preliminary data (just the punchline), and work by others if relevant.* |

Specific Aims: *The aims paragraphs should each contain minimally a title and a working hypothesis. These should make it clear which component of the central hypothesis is tested in that aim—and why. Each title should be broad and open-ended; the working hypothesis can provide the focus of the aim. If you have no room to expand on how you will achieve your aim in an additional sentence or two, make sure that your working hypothesis gives a sense of approach and readout.*

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| **Aim 1: Title**  Working hypothesis: | **Aim 2: Title**  Working hypothesis: |

Payoff

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| Expected outcomes: *What your aims are likely to produce, how that would contribute to the overall objective, and what broader impact this would have on this area of research AND/OR how will this help you fulfill your career goals.*  How   * “The *expected outcomes* are …”   Broader impact AND/OR Career impact   * “The *broader impact* is….” AND/OR “The proposed project will provide me with…” |

**Research Training Project Strategy**

**Scientific Foundation and Rationale** (subsection): *(1–1.5 pages) Place the proposed work within the context of the overall mission of the funding agency, justify the need for what you propose, explain previous findings on which you base your studies (including their rigor), and indicate the positive effect that completing the project will have on the problem you are addressing.*

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| Importance of the problem: *An extension of the information provided in the first paragraph of the Specific Aims page, e.g., what problem or critical barrier your research addresses (substantiated with documentation from the literature) and the negative consequences of not meeting the need. Be sure to go from* ***broad to specific****; do not interrupt the flow with a statement of what you plan/expect to accomplish—save this for the* ***Significance of the expected research contribution*** *subsection below.*   * Opening sentence/problem being addressed… * “It is widely appreciated that…” * “There is a clear lack of…” * “Thus, there is an *urgent need*…”   Scientific context and rigor of prior research (previously, scientific premise): *The foundation on which your proposal is built and your evaluation of how reliable it is.* ***Organize by aim or overall.*** *Discuss: the strengths and weaknesses in rigor of the prior research (both published studies and unpublished preliminary data) that serves as the key support for the proposed project. Note that it may be more appropriate to discuss limitations rather than issues with rigor. End by including general statements (leave details for Approach section) about how weaknesses of prior research will be overcome. Cite only the strongest supporting publications.*   * “Numerous studies have…” * “However, studies X and Y have important limitations…” * “In addition, the rigor of study Z is not sufficient in that the antibody…” * “To overcome these limitations/gaps in rigor, we will…” **[keep this general]** * “Thus, our proposed studies will circumvent the limitations of…by…”   Significance of the expected research contribution: *The research contributions you expect to make; these should be relevant to the mission of the funding agency. Write about contributions to science in general vs. your field separately as suggested below, or in a single paragraph. In each paragraph your argument should go from* ***specific to broad.***   * Impact of the project on scientific knowledge: *How the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more fields.* * Impact of the project on the field: *How the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be advanced (vertically) if the proposed aims are achieved.* |

**Approach** (subsection):

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| **Issues related to rigor & reproducibility:** *For paragraphs on* ***Addressing weaknesses in rigor of prior research,******Strategies to ensure rigor of the proposed research*** *and* ***Considerations of biological variables including sex****, authors should provide relevant information that clearly addresses all points. This can be done:*   * *at the beginning (as shown below) or end of the Approach subsection (advisable if applicable to all aims), or* * *in each aim (if information differs by aim).*   *The key is to make all information on the topic of R&R easy to find, i.e.,* ***the paragraphs should be labeled****.*  Addressing weaknesses in rigor of prior research **–** *(0.25 pages)*  *Describe plans to address weaknesses in rigor of the prior research that serves as the key support for the proposed project.*   * “As described under Significance, the key weaknesses of past studies of xxx are yyy.” * “In the current study, we will address xxx.” * “In addition, we will ensure the proposed research is performed rigorously, as described below.” |

**Research Training Project Strategy (cont.)**

**Approach** (subsection cont.):

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| Strategies to ensure rigor of the proposed research – *(0.25 pages)*  *Describe how you will ensure a robust and unbiased approach appropriate for the work proposed. Strategies may include:*   * *Randomization protocol for sample groups* * *Blinded data recording and analysis* * *Controls and replicates needed* * *Sample size estimation/power analysis (critical for studies using human subjects or higher vertebrates)* * *Principles of Good Laboratory Practice* * *Essential reagents and their authentication* * *Statistical analyses to be used*   [Adapted from Landis SC et al. (2012) A call for transparent reporting to optimize the predictive value of preclinical research. *Nature* Oct. 11; 490(7419):181-91.](https://www.ncbi.nlm.nih.gov/pubmed?term=nature%5BJour%5D+AND+2012%5Bpdat%5D+AND+landis%5Bauthor%5D&cmd=detailssearch)  Consideration of biological variables, including sex, in the proposed research – *(0.25 pages)*  *Include discussion of:*   * *Sex (required; e.g,. inclusion of equal numbers of each; sex impact on results; separate analysis of results; karyotype of cell lines)* * *Weight, age, and health status, if applicable* |

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| **Aim** **1:** *Title to be repeated verbatim from Specific Aims page.*  Introduction: ***Include the following points, combined into one paragraph of ~6-8 sentences.***   * Justification: *The question/problem that needs to be addressed (a part of the overall need).* * Objective of Aim: *Part of the overall objective stated on Specific Aims page; also how attaining this objective will help address/resolve the question posed above.*   + “The *objective* of this aim is to…” * Working hypothesis: *Repeated verbatim from Specific Aims.*   + “To attain this objective, we will test the *working hypothesis* that…” * Approach: *The approach you will use to test your working hypothesis.*   + “Our *approach* to testing the working hypothesis will be…”   Justification and feasibility: *Preliminary data and findings from the literature that support the rationale of this aim.*   * Preliminary data/data from the literature: * Rationale: *Future steps that will only be possible after the proposed work is completed. Include preliminary data that strengthen your rationale.*    + The *rationale* for this aim is…   Research design:   * Subaim 1*Possible details to include – not an exhaustive list. Include statements on achieving robust and unbiased results and considerations of biological variables if not provided as a separate paragraph.* * *Approach to be used* * *Overview of methods* * *Essential minor/major equipment* * *Detailed expectations* * *How results will be interpreted* |

**Research Training Project Strategy (cont.)**

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| * Subaim 2*(as above)*   Expected outcomes:*Short paragraph that integrates outcomes from all proposed activities within this aim, and indicates how they will contribute to achieving your overall objective.*  Potential problems and alternative strategies:*Essential for every aim. Propose alternatives in case your hypothesis is proven invalid/critical reagents fail/approaches are inconclusive. These problems should not be major; even if they occur, the alternatives described here should enable you to achieve the main objective of your proposal.* |

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| **Aim 2:** (as above) |

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| **Timeline and benchmarks for success:** *Preferably in table format (makes it easy for reviewers to visualize). Demonstrate that you have thoroughly considered how long it will take to complete each subaim. Include when you expect to achieve certain benchmarks (be sure to specify what these are). See examples* [*here.*](https://sercc.medicine.uiowa.edu/sites/sercc.medicine.uiowa.edu/files/2023-12/Timeline_Template_2022_03_11.docx) |

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| **Future directions:** *Brief summary of where you expect the science to be at the conclusion of the proposed research. Include the next expected steps and why they are important.* |

**Specific Aims Page**

Multiple Sclerosis (MS) is an autoimmune disease characterized by demyelination of neurons in the central nervous system, and one of its most common clinical presentations is high levels of fatigue. This disease takes a heavy toll in that xxx. Notwithstanding its impact on society and extensive efforts to xxx, little is known about the underlying causes or how to ameliorate the symptoms and improve the quality of life for patients. Currently, one of the few available clues is a link between lipid intake by patients and a reduction in fatigue. This is based on a study in which 19 MS patients adhered to a paleolithic diet for 12 months and reported a dramatic reduction in levels of fatigue. The specific physiological reasons for the change in this set of patients on the “Wahls diet” is unknown, in large part because of the complexities of analyzing metabolic data in combination with the small size of the patient population. However, metabolomic data suggest that changes in lipid profile are associated with severity of clinical symptoms experienced by patients with MS. I contend that improvements in statistical analysis will make it possible to address the following *critical need:* to identify key changes in the metabolism that are the underpinnings of disease, in MS patients and others.

My *long-term goal* as a physician scientist is to statistically identify metabolic imbalances associated with fatigue levels observed in patients with MS. The main *objective of the proposed research* is to develop a statistical methodology that will make possible a meaningful analysis of metabolomics data, which by its nature is highly dimensional, i.e., for which the number of samples collected is smaller than the number of variables. Specifically, I propose to develop a penalized regression method with less bias than those typically in use, to provide more accurate analysis and make possible the identification of the lipids that account for the changes in patient fatigue. My *central hypothesis* is that use of an adequate penalty criterion in the regression model will make it possible to determine which specific lipid changes make the main contribution to the improved levels of fatigue seen in MS patients who participated in the Wahls diet. The *rationale* for undertaking this study is that developing a more accurate penalty criterion will improve existing penalized regression models and, when applied to this data set, make it possible to identify specific metabolic imbalances in patients with MS and tjis guide personalized treatment.

**Aim 1: Design a Penalty Criterion that is Adequate for the Penalized Regression Methods**

Current penalization criteria use a constant to constrain the value of estimates in regression models, and for highly dimensional samples this leads to strongly biased estimates. I propose to design a penalty function instead of a penalty constant, which will make it possible to assign specific penalties to each variable. I will develop the mathematical foundation of this penalty function and compare its performance on a set of 19 MS patients and 19 controls to that of current methods, using metabolic data documented in the literature.

**Aim 2: Identify Lipids Associated with Fatigue Levels in Patients with Multiple Sclerosis**

Although current penalized regression methods give biased estimates when samples are small and highly dimensional, they can nevertheless provide information about the overall importance of the variables that are being analyzed should the development of more effective methods prove a challenge. Thus, I will apply current as well as newly developed methods of penalization to the Wahls diet data set, and identify the lipids that are associated with changes in fatigue levels in these MS patients. Lipids will be identified by sequencing using mass spectrometry, followed by application of the various regression models to explain the variability of fatigue as a function of the lipid profile.

The *expected outcomes* of the proposed research are a new type of penalty criterion that will both improve the accuracy of analysis of data from small samples with high dimensionality and make it possible to identify specific metabolic imbalances in patients with MS. The *broader impact* of these discoveries will be progress in the treatment of MS, as well as in the study of complex diseases more generally. The *impact on my career goals* will be preparation for my role as a physician scientist, providing me with skills in statistical methodologies that can be applied to a broad range of conditions.