

INBRE Grant Writing Workshop: Significance and Innovation

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The Basics

White space is your friend

- Easier on the reviewer to read
- Demonstrates your ability to write concisely
- Space between paragraphs
- Indent paragraphs
- Use headings or bullets to summarize

1. Significance

CARD11-driven BCR signaling is a key pathway in DLBCL:

Failure to respond to initial or salvage chemotherapy occurs in almost half of DLBCL patients, most of which progress or relapse within the first two years of diagnosis.^{9,10} These aggressive DLBCL are marked by constitutive tumor growth and survival that is often due to hijacking of the BCR pathway.^{1-3,5} In particular, the activated B-cell (ABC) subtype and three recently identified DLBCL subtypes from new molecular classifications exhibit BCR-associated gene expression profiles that are tightly linked to poor patient outcome.^{5,9,10,12} Although there are several components to the BCR pathway, recurrent gain-of-function mutations in *CARD11* are frequently found in these chemoresistant DLBCL.^{3,5,6,12} When mutant forms of *CARD11* are forcibly expressed in DLBCL cell and mouse models, an enhanced, uncontrolled proliferation occurs leading to lymphomagenesis as work using RNA interference in ABC DLBCL results in severely compromised cell viability.^{3,7} These findings strongly suggest DLBCL has an addictive survival reliance on *CARD11* expression. Thus, targeting this oncogenic pathway in this lymphoma is a promising av

Barriers to eliminating BCR signals: The effectiveness of precision medicine is often hindered by drug resistance due to target mutation, upregulation of the target protein, and/or alternative signaling pathways. To date, designing therapeutic interventions to target the BCR pathway for inhibiting the BCR signals.¹³ In spite of success in inhibiting Bcr2a



READ THE INSTRUCTIONS!

From the NIH SF424 Instructions

<https://grants.nih.gov/grants/how-to-apply-application-guide.html>

Use them as a guideline/outline – do not be afraid to use the same verbiage

(1) Significance

- Explain the importance of the problem or critical barrier to progress that the proposed project addresses.
- Describe the strengths and weaknesses in the rigor* of the prior research (both published and unpublished) that serves as the key support for the proposed project.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.
- The strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. This includes full transparency in reporting experimental details.

What is the purpose of the Significance?

To tell the Reviewers the importance of the problem and how the proposed research project will improve scientific knowledge and how the field will be changed (via your newly proposed concepts, methods, technologies, treatments, services, or preventative interventions) – while highlighting how previous research has missed the mark.

- Recommended Length: Approximately 1-2 pages (approx. 1 page for 6-page research plan; 2 for 12-page research plan)
- Content: The Significance section replaces the previous Background and Significance section.

It should cover:

1. The state of existing knowledge, including literature citations and highlights of relevant data (yours and others)
2. Rationale of the proposed research
3. Explain gaps that the project is intended to fill
4. Potential contribution of this research to the scientific field(s) and public health.

Applicant Instructions and Reviewer Criteria are essentially the same – Read and write to those too!

From the Parent Announcement Scored Review Criteria

***NIH new simplified review criteria combines Significance and Innovation: IMPORTANCE OF THE RESEARCH

Keep in mind, an application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

- Does the project address an important problem or a critical barrier to progress in the field?
- Is the prior research that serves as the key support for the proposed project rigorous?
- ***If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?***
- ***How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?***

Suggestions:

- Establish significance through a careful review of published data in the field, including your own. Avoid outdated research. Use citations not only as support for specific statements but also to establish familiarity with all the relevant publications and points of view. Your application may well be reviewed by someone working in your field or not.
- Highlight success of your related grants/manuscripts and awareness of potential barriers and alternative approaches
- Highlight why research findings are important beyond the confines of a specific project i.e., how can the results be applied to further research in this field or related areas
- Clearly state public health implications
- Relate back to the hypothesis

**Do not shy away from being explicit –
“This project is significant because...”**

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(2) Innovation

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation or interventions.
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation or interventions.

What is the purpose of the Innovation?

To tell the Reviewers how your project will advance the field through knowledge or technology – what is NEW.

- Typically ¼ - ¼ page

D. Innovation

Previous gene expression profiling of adult DLBCL generated an understanding of the clinical heterogeneity (14-16), however not always correlate as post-transcriptional and –translational events can in is translated into protein (21,22). Since protein is the functional effector m therapeutics target proteins, mRNA expression requires validation at the establish a systems biology model in which both genomics and prote bioinformatics to effectively tease out the greater biological picture that implement a comprehensive and integrative approach by:

- using cutting-edge proteomic TMT labeling MS technology in parallel bioinformatics analyses across platforms and;
- offering an alternative drug targeting strategy of direct transcription in structure alone and in combination with PAK1 inhibition.

We will determine the expression of the largest panel of genes and proteins to date in p compared to adult DLBCL. Our findings will identify pathogenic pathways utilized in the in pediatric patients and provide several lines of scientific discovery to pursue in futur

2. Innovation

Our proposed work is *conceptually innovative* by examining an un The current field investigating the oncogenic function of NEK2 is large such as hepatocellular and colorectal carcinomas, and one hematolog minimal efforts focused on NEK2 cancer-enabling activities in lymph patients. In identifying NEK2 as an integral signaling molecule in th advance our understanding of the molecular pathways that define these 1, explores a *new approach* to leverage a bifunctional small mo degradation with potential to overcome resistance mechanisms frequ Additionally, this strategy allows us to test the contributions of th interactions of NEK2 in eliciting and maintaining pro-tumor phenotype will produce an instrumental tool to comprehensively study NEK2 in A

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INNOVATION

This study shifts the current focus of AYA DLBCL research by investigating an u NEK2-dependent signaling in AYA DLBCL. We will use advanced technologies to der integral signaling molecule in regulating survival pathways in AYA DLBCL and develop approach to study this oncoprotein.

Conceptual Innovation:

NEK2 is recognized to regulate aspects of the cell cycle, chromosomal instability, ar solid tumors including breast and lung carcinomas, as well as in the hematologica myeloma (20). These findings set the precedence of an oncogenic role for NEK2 knowledge of how NEK2 functions in AYA lymphoma is limited by the lack of research setting. We propose NEK2 activity is central to the oncogenic signaling in AYA DL molecular pathways that underlie the tumor biology of DLBCL in AYA patients, foundational understanding of this disease to incite new studies and the development of

Technological Innovations:

1) Most kinase inhibitors target the ATP binding pocket to prevent the catalytic tra substrates (42). This approach has led to the successful treatment of several can inhibits kinases with cancer-promoting activity beyond catalysis, such as NEK2. In co proteolysis-targeting chimera (PROTAC) strategy for removal of NEK2 from a tum complete inhibition and functional characterization of NEK2 activity. While PROTACs proteins and kinases, NEK2 has not been targeted for PROTAC degradation. Our

by examining an un action of NEK2 is large as, and one hematolog ling activities in lymph signaling molecule in th ways that define these bifunctional small mo ce mechanisms frequ e contributions of th pro-tumor phenotype vely study NEK2 in A

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Innovation

- Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?
- Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?
- Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Suggestions:

The innovation section should include the following: Explain why **concepts** and **methods** are novel to the research field. Focus on innovation in study design and outcomes.

- Describe how the application differs from current research or clinical practice paradigms
 - Even if using a standard or well-known approach – are you using it in a new way?
- Carefully review of the current literature to support the innovative methodologies, approaches, or concepts of your research – to make an accurate statement of how your proposed work differs
- Demonstrate familiarity with novel methodologies by citing your publications and publications of others in the field
- Summarize novel findings to be presented as preliminary data in the Approach section
- Relate back to the hypothesis

Reflection exercise prior to writing:

- What is the problem you seek to address?
- Why is it important?

} Significance

- How do you plan on addressing the problem?
- What will we get?
 - Products/insights
 - New data sets (proteomics, RNAseq),
 - Reagents you make (engineered cells or animals, antibodies etc)

} Innovation

What (Aims)	How (Approach)	Products (Impact)	Why important (Impact)
<p>To determine if collagen cleavage by TAF-expressed FAP induces SR-A-mediated macrophage M2 polarization and release of fibroblast activators.</p>	<p>Fibroblasts isolated from normal and tumorous breast tissue will be used to modify collagen in vitro. Macrophages will be adhered to these matrices and the resulting phenotype assessed by examining markers associated with M1 and M2 phenotypes. The importance of FAP activity will be determined using recombinant FAP and FAP specific inhibitors. Macrophages isolated from SR-A^{+/+} or SR-A^{-/-} mice and COX inhibitors will be used to confirm the involvement of SR-A and COX in M2 polarization. Fibroblasts will be exposed to SR-A^{+/+} or SR-A^{-/-} macrophages adhering to FAP-modified, TAF-modified or untreated collagen and then scored for markers of activation.</p>	<p>Roles of SR-A; FAP and signaling pathways they impact will be identified.</p> <p>TGF-β from macrophages (activates fibroblasts), INFγ/LPS (M1 inducer); IL-4 (M2 inducer) and then relationship to macrophages binding to FAP-leaved collagen.</p> <p>(we only had concept-products in this aim – but there might be RNAseq or proteomic data sets. If you were producing antibodies or engineered cells these would all be products potentially useful to the scientific community)</p>	<p>The research will determine key molecular and cellular events mediating macrophage retention in tumors and the polarization of TAMs to an M2 phenotype. Maintenance of the M2 phenotype by a positive feedback loop involving TAFs will also be investigated. Disruption of a positive feedback loop that drives TAM retention and M2 polarization might relieve immune suppression and inhibit tumor progression.</p>