



K Award Research Plan

Guidance & Tips

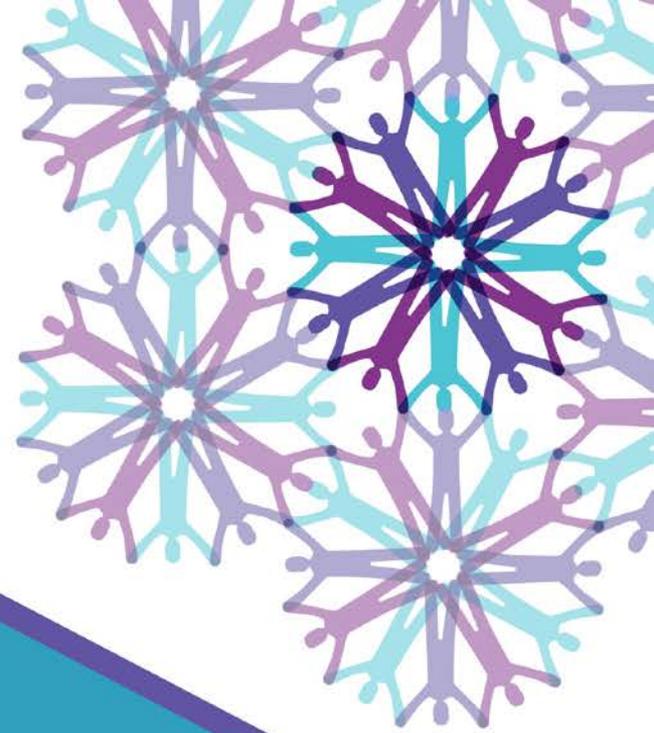
| CENTER TO REDUCE
CANCER HEALTH DISPARITIES

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Outline

- *Specific Aims*
- *Research Strategy*
- *Training in the Responsible Conduct of Research*





Specific Aims

Anatomy of a Specific Aims Page

- Introduction and the gap in knowledge
 - Explain what is currently known and identify the gap area
 - Explain why it is critical to perform this research
- Solution to fill the gap in knowledge
 - What do you want to do – what is the scientific premise?
 - Why are you doing it – create a central hypothesis or conceptual framework
- Describe each of the aims you will use to test your hypothesis (3 - 4 aims)
 - Aims to examine the hypothesis should be related, but not inter-dependent
 - In 2-4 sentences, describe how each aim will help to answer your larger hypothesis
 - Briefly describe the approach to be taken
- Provide the final summary paragraph
 - Expected Outcomes, Long-term goal of the application, Impact on your career development

Specific Aims: **Sample** Introduction, Background, & Gap

- Latina women in the US have lower incidence of breast cancer compared to African American, or non-Latina white women.
- However, US Latinas have lower survival rate than non-Latino whites. Breast cancer incidence varies greatly across Latin America, and it has been suggested that this variation is due to differences in genetic ancestry, lifestyle and environmental factors. Our own data has shown that higher European ancestry is associated with higher breast cancer risk among US Latinas and Mexicans.
- The degree to which the association between genetic ancestry and breast cancer risk among Latinas is due to genetic vs. non-genetic (environmental, reproductive dietary) factors remains unknown.

Specific Aims: **Sample** Hypotheses

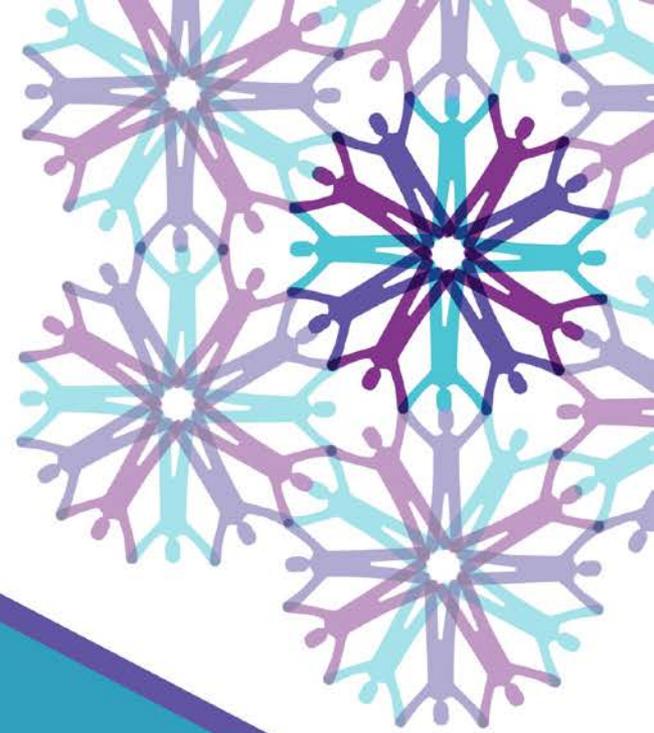
- The main hypotheses driving the present study are:
 - Differences in breast cancer risk and mortality between populations are partially driven by the action of multiple common genetic variants with small effects
 - These genetic variants affect risk for particular tumor subtypes
 - Some of the genetic variants that affect tumor-subtype specific risk are different from the variants that drive cancer recurrence and metastasis

Sample Specific Aims

- We will test these hypotheses with the following specific aims:
 - Specific aim 1: Identify common genetic risk variants for breast cancer subtypes in Latinas. Genotypes from approximately 900,000 experimentally typed and 1,500,000 imputed single nucleotide polymorphisms (SNPs) will be evaluated for association with particular breast cancer subtypes in a sample of 1,600 US Latinas with breast cancer and 1,300 controls.
 - Specific aim 2: Identify common genetic risk variants for breast cancer stage at diagnosis and breast cancer specific survival in Latinas. Available data on stage at diagnosis and survival from 1,600 Latina women with breast cancer will be analyzed in association with the above-mentioned 2,400,000 SNPs.

Specific Aims: Application Tips

- The Specific Aims page should capture your entire application
- Start by setting the context and funnel down to the problem and solution
- Create a solid hypothesis with a strong scientific premise
- Use 3-4 realistic aims over 3 to 5 year funding period, with the resources available otherwise may be considered too ambitious
- Conclude with an impact statement
- You need to gain the reviewers' confidence while convincing them that your proposal is important to fund
- Use *italics*, **bold**, underline to emphasize key points in the SA page (in moderation) and be consistent throughout the application



Research Strategy

Significance, Innovation, & Approach

Research Strategy: Significance

- Half to three-quarter's of a page in length
- Explain the importance of the problem or critical barriers to progress that the proposed project addresses
- Describe the scientific premise for the proposed research, including consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application
- Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that impact the field will be changed if the proposed aims are achieved
- Explain how the proposed project will help you achieve your goals to be an independent R01-competitive researcher

- Research Strategy:
 - ✓ ***Significance***
 - Innovation
 - Approach

Research Strategy: **Sample** Significance

Importance/
scientific premise



2. Research Strategy

2.1 Significance

In the U.S., Latinos are the largest, youngest and fastest growing minority population, accounting for 15% of the nation's total population. Currently, there are 42.6 million Latinos in the U.S., not including residents of Puerto Rico. By the year 2050, it is predicted that 25% of the U.S. population will be Latino⁵⁰. However, Latinos are dramatically under-represented in biomedical studies. Our proposal is the first genome wide association study of breast cancer subtype and survival in Latinas. If we identify novel genetic variants that are associated with survival or with tumor subtype specific risk, these variants may be in genes and biological pathways that are previously unrecognized to be involved breast cancer progression. These pathways may be new targets for breast cancer treatment. In addition, our proposal is also the first of its kind in Latina women to evaluate germline genetic variants associated with tumor subtype defined by microarray. Microarray analysis allows a more refined tumor subtyping compared with histological subtypes. In particular, luminal type A (associated with excellent prognosis) and luminal type B (associated with poorer prognosis) cannot be discriminated on the basis of clinically available histological markers. If a particular genotype is associated with luminal type B, women with this genotype may be candidate for more aggressive screening to improve early detection.

Project impact



This proposal is a natural extension of the recently developed US-Latin America Cancer Research Network (US-LACRN), established by the Office of Latin America Cancer Program Development at NCI. This proposal will make use of the already developed infrastructure for tumor collection and analysis and add to it a germ-line genetics/ancestry component. The two projects together will generate the first study of breast cancer genetics (both at the tumor and germ-line level) in Latin America and will significantly improve our understanding of breast cancer etiology and progression in Latinos. Furthermore, it will set a model for future studies of breast cancer in the rest of Latin America.

Project & research
independence



Finally, this proposal will provide the training, mentorship and preliminary research to allow Dr. [REDACTED] to develop into an independent breast cancer researcher focusing on Latino populations. Her career development will help diversify the work force in academic biomedical research and bring an expert with both technical and cultural expertise to address important research questions in breast cancer in this population.

Since the first reported GWAS results for breast cancer, many common new variants have been discovered and replicated²⁸. Despite the small effect of those variants, identifying all of them will contribute to our understanding of the increased risk of breast cancer in first-degree relatives of affected women and it will increase our understanding on the key pathways that contribute to breast carcinogenesis.

Research Strategy: Innovation

- Begin the section with “the proposed research is innovative because.....”
- Present a new and substantially different way of addressing an important human health-related problem
- Explain how your application challenges 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 processes
- Present how the results from this proposal will contribute significantly to existing knowledge -base

- Research Strategy:
 - Significance
 - ✓ ***Innovation***
 - Approach

Research Strategy: **Sample** Innovation

- Multiple genome wide association studies (GWAS) for breast cancer have been conducted to date. Through these efforts, there are now approximately 18 known common genetic variants with small effects that contribute to disease risk.
- However, **all previous studies included samples of European or Asian women and none of them was conducted using samples of Latinas.** Furthermore, only a couple of studies evaluated if the discovered risk variants had a different effect depending on hormone receptor status of the tumor and only one GWAS was conducted looking at breast cancer specific survival and progression. We are currently in the replication stage of the first GWAS in Latinas, which includes a total of 2,900 women (1,300 controls and 1,600 cases). We have access to information about disease stage for the cases we have genotyped as well as information on the tumor's hormone receptor status.
- Therefore, we are proposing to conduct the **first GWAS study in US Latinas** taking into account tumor subtypes determined by hormone receptor status (Aim 1) and the first metastasis and survival GWAS (Aim 2).

Significance & Innovation: Application Tips

- Limit both subsections to one page in length
- The purpose of the Significance and Innovation subsections is to help justify the need for the proposed research
- The audience (reviewers) is busy, may not know your field in detail, and may be skeptical
- Present your ideas and arguments so they can be comprehended with the least amount of mental effort and time

Research Strategy: Approach

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project
- Describe the experimental design and methods proposed and how they will achieve robust and unbiased results
- Show how biological variables have been factored into study design
- Include how data will be collected, analyzed, and interpreted
- Discuss potential problems, alternative strategies, and benchmarks for success
- Show the power analysis for your study indicating how the number of samples analyzed will be powered
- Include preliminary data to establish feasibility

- Research Strategy:
 - Significance
 - Innovation
 - ✓ *Approach*

Suggested Organization of the Approach Subsection (A)

- Introduction
- Background (include graphics for comprehension)
- Preliminary data (legible diagrams and figures)
- Research design for each aim
 - Study design, procedures, methods
 - Data quality control, reproducibility and rigor
- Expected outcomes, benchmarks for success
- Potential problems and alternative approaches
- Timeline of activity
- Future directions to an R01-competitive research program

Suggested Organization of the Approach Subsection (B)

- For each aim
 - Background (include graphics for comprehension)
 - Preliminary studies (legible diagrams and figures)
 - Research design for each aim
 - Study design, procedures, and methods
 - Data quality, reproducibility, and rigor
 - Expected outcomes and benchmarks for success
- Potential problems and alternative approaches
- Timeline of activity
- Future directions to an R01-competitive research program

Preliminary Data

- Should be relevant to the proposed research plan
- Demonstrate feasibility/availability of resources and critical reagents, ability to recruit proposed population, access to database
- Supports the scientific premise

Sample Timeline

2.4 Timeline and (%) of time devoted to each activity

Research and didactic activities	Year 1	Year 2	Year 3	Year 4	Year 5
Specific aim 1: Analysis of US Latinas GWAS data by hormone receptor status	X (20)				
Specific aim 2: Analysis of US Latinas GWAS of breast cancer stage and survival		X (60)	X (5)		
Specific aim 3: Replication in samples from Argentina			X	X	X
Genotyping of 192 NPs in 600 samples from Argentina			X (30)	X (2)	
Analysis of tumor subtype specific risk variants in Argentina				X (38)	X (30)
TICR certificate courses (see training plan for details)	X (70)				
Grant writing course/Responsible conduct of research course (see training plan for details)		X (2.5)	X (2.5)	X (2.5)	
Teaching within the TICR program (as well as mentoring students during last year of K award)			X (8)	X (8)	X (8)
Seminars related to the UCSF K-scholars program and others	X (5)	X (10)	X (7.5)	X (7.5)	X (7.5)
R01 writing and submission (as well as writing other grants during last year of K award)			X (25)	X (20)	X (20)
Preparation and submission of manuscripts and dissemination of results for clinical practice & public health		X (20)	X (15)	X (15)	X (27.5)
Meetings in [REDACTED] with collaborators		X (2.5)	X (2.5)	X (2.5)	X (2.5)
Meetings with Dr. [REDACTED]	X ¹ (2.5)	X ¹ (2.5)	X ² (1.25)	X ² (1.25)	X ² (1.25)
Meetings with Dr. [REDACTED]	X ² (1.25)	X ² (0.65)	X ² (1.25)	X ² (0.65)	X ² (0.65)
Meetings with other collaborators	X ^{an} (1.25)	X ^{an} (1.85)	X ^{an} (2)	X ^{an} (2.6)	X ^{an} (2.6)

1-8: Indicates every how many weeks the meetings will take place. "an" indicates meetings will occur as needed.

Approach Subsection: Application Tips

- **Avoid** a narrow focus on a single pathway without appreciation of alternative explanations
- **Refer** to published related work and methodology, and **cite** your preliminary data, if published
- Describe the **relationship** between the mentor's research and the candidate's proposed research plan
- **Differentiate** your research project from your mentor's to create a niche area that will be portable
- Convey this research plan is **well-positioned** to transition into an independent R01 competitive research program

Fatal Flaws: Actual Reviewers' Comments

- The rationale for the experiment is *weak*, or scientific premise is **not** convincing. *Feasibility* is **not** demonstrated.
- The candidate's training plan, mentors' expertise, and the candidate's research plan are *not aligned*, i.e., engaging in the research plan without appropriate training
- The approach for statistical analysis including all parameters is **not well described or powered**
- The human subjects and research plan are *vague* and **without clear end-points** to evaluate the efficacy of the proposed intervention
- *Expectations* and *potential problems* **not** included for each aim
- Proposed research is *overambitious* and not realistic

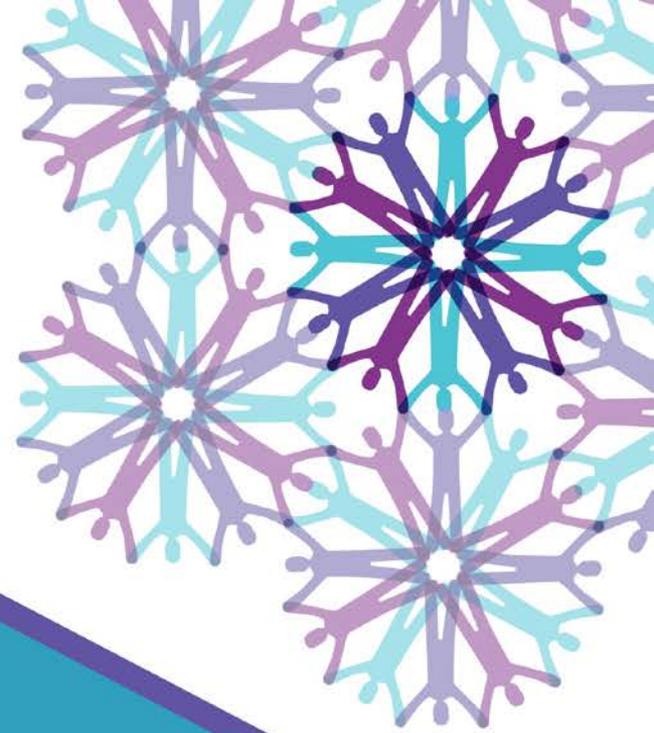
Happy Candidate: Actual Reviewers' Comments

- Dr. Doe is a committed **strong candidate with high quality** prior training, research experience and research productivity
- CDP is **well-integrated with research and mentoring** plans
- Proposed research plan is hypothesis-driven and **feasible, strong premise**, and built upon candidate's prior training
- Research plan is supported by **strong preliminary data**
- Research plan can ideally serve as a **training vehicle for research independence**
- Collectively, this strong application will deliver **outstanding overall impact**

Research Plan Summary

- The research component should be driven by a strong scientific premise (background and preliminary data), and hypotheses rather than advances in technology
- Proposed research must be consistent and aligned with the career development goals, and experience level of the candidate
- The research plan is a vehicle for research independence
- The research and other developmental activities should provide the necessary experience, knowledge, and skills, to lead to an independent R01-competitive research program

Training in the Responsible Conduct of Research



Training in the Responsible Conduct of Research

- One-page in length
- Is the plan appropriate for your career stage?
- Will it enhance your understanding of the ethical issues in research?
 - **Format:** coursework, seminars, online
 - **Subject Matter:** research ethics, human subjects, COI, publications ethics
 - **Faculty Participation:** faculty led programming with face to face interaction
 - **Duration of instruction:** semester long, 6 weeks
 - **Frequency of instruction:** available all year, fall semester only

Other Research Plan Subsections

- Resource sharing plan
- Protections for human subjects
- Inclusion of women, minorities, and children
 - Must justify the proposed distribution of individuals (gender, race/ethnicity) in the sample
- Vertebrate animals use justification and care: address all 5 points
- Hazardous materials and precautions to be exercised
- Justification if not using an approved human Embryonic Stem Cell line from the NIH hESC Registry



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