The American Cancer Society's mission is to save lives, celebrate lives, and lead the fight for a world without cancer.

The Melanoma Research Alliance (MRA) mission is to end suffering and death due to melanoma by collaborating with all stakeholders to accelerate powerful research, advance cures for all patients, and prevent more melanomas.
AMERICAN CANCER SOCIETY-MELANOMA RESEARCH ALLIANCE
RESEARCH FOR PROPOSALS: UNDERSTANDING, PREVENTING AND MANAGING IMMUNOTHERAPY-RELATED ADVERSE EVENTS (irAEs) ASSOCIATED WITH CHECKPOINT INHIBITION FOR MELANOMA AND OTHER CANCERS

PILOT AWARD POLICIES

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1. OVERVIEW
The American Cancer Society (ACS) and the Melanoma Research Alliance (MRA) have partnered to support research leading towards reduction of immune related adverse events (irAEs) and improvement of overall outcomes for cancer patients treated with checkpoint immunotherapy.

About American Cancer Society
The American Cancer Society is a global grassroots force of 2 million volunteers saving lives in every community. As the largest voluntary health organization, the Society's efforts have contributed to a 25 percent decline in the cancer death rate in the U.S. since 1991, driven by less smoking, better treatments, and earlier detection. We're finding cures as the nation's largest private, not-for-profit investor in cancer research, ensuring people facing cancer have the help they need and continuing the fight for access to quality health care, lifesaving screenings and more.

About Melanoma Research Alliance
The Melanoma Research Alliance (MRA) is a public charity formed in 2007 under the auspices of the Milken Institute, with the generous founding support of Debra and Leon Black. The mission of MRA is to end suffering and death due to melanoma by collaborating with all stakeholders to accelerate powerful research, advance cures for all patients, and prevent more melanomas. MRA is the largest private funder of melanoma research. MRA funds research projects worldwide to make transformative advances in the prevention, diagnosis and staging, and treatment of melanoma.

2. RESEARCH AWARDS TO BE FUNDED BY THIS PARTNERSHIP
This Request for Applications (RFA) is intended to provide support for pilot or exploratory projects whose purpose is to test interventions, develop research methodologies and explore novel areas as defined in the RFA.

3. APPLICATION DEADLINE:
Applications for grants and awards must be submitted as paper and electronic copies via proposalCENTRAL. Access is available using links provided in the American Cancer Society web site www.cancer.org (see Instructions). The electronic applications must be submitted at the proposalCENTRAL website by close of business (5:00 PM EST) on the specified deadline date. For the convenience of the applicant, a paper copy is due one day after submission of the electronic copy. No supplemental materials will be accepted after the deadline unless requested by staff for administrative purposes or when requested by the reviewers.

4. ELIGIBILITY

A. Eligibility Requirements:

1. Eligible Institutions: Applications may be submitted by a college, university, medical school, or not-for-profit research organization within the United States, its territories and
the Commonwealth of Puerto Rico. A not-for-profit institution is one that –IF REQUESTED- can provide:

- A current letter from the Internal Revenue Service conferring 501(c)(3) status,
- Documentation of an active cancer research program

Unsolicited grant applications will not be accepted from, nor will grants be made for, the support of research conducted at for-profit institutions, federal government agencies (including the National Laboratories), or organizations supported entirely by the federal government or organizations, such as Foundations operated by, and for the benefit of, Veteran Affairs Medical Centers, whose primary beneficiaries are federal government entities. Applications may be submitted by qualified academic institutions on behalf of Veteran Affairs Medical Centers, if a Dean’s Committee Memorandum of Affiliation is in effect between the two institutions.

2. Eligible Applicants: Independent investigators at all stages of their career are eligible to apply. Principal investigators (PI) must hold a doctorate degree (M.D., Ph.D., or equivalent) and have a full-time faculty position or equivalent at a college, university, medical school, or other not-for-profit organization within the United States. Multiple PIs or Co-PIs are not allowed.

5. EVALUATION OF APPLICATIONS
The overall impact of the proposed research will be assessed using the review criteria to assess the scientific merit, the translation nature of the proposed research and the degree to which the research has rapid clinical benefit.

Applications will be evaluated on the following criteria:

Significance
Does the project address an important problem or a critical barrier/need to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice improve? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Cancer Relevance
How is this research relevant to persons at risk for irAEs, being treated with checkpoint inhibitors or who are experiencing early or late effects?

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?
Investigators
Does the PI and research team have the training and experience needed to carry out the proposed research? Does the research team have the complementary skills and qualifications needed for successful implementation and analysis of the proposed research?

Approach
Is the study design appropriate to address the specific aims? Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well-reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Are potential problems, alternative strategies, and benchmarks for success presented? How will the strategy to establish feasibility and particularly risky aspects be managed? Are plans for data collection and analysis well-reasoned? Do investigators include relevant limitations? Is the sample size sufficient? Are study timelines feasible to carry-out the scope of work and do plans for future research represent a meaningful and logical extension of the proposal under review?

Environment
Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, collaborative arrangements or emerging technologies?

Potential for Future Funding of Project: A clearly defined plan regarding future use of study findings to pursue subsequent funding is an integral part of this mechanism. Is there a clearly defined plan regarding how the data and/or process information generated will be used to develop a larger, extramurally funded project?

6. TERMS OF THE AWARDS
Research Intent, Budget and Award Period
Potentially transformative early studies that will form the basis of future research will receive a Pilot Award of $200,000 total for a 2-year period of performance. Fellows, others in training or those in research support positions are not eligible to apply. Pilot Award proposals are not required to contain extensive preliminary data, but must articulate a strong hypothesis and translational goals. Up to five (5) Pilot Awards will be made under this RFA. Proposals should include some aspect of melanoma research but need not be limited to this disease area. The PI must budget some percent effort.
7. **GRANT MANAGEMENT AND PAYMENTS**

New grantees will receive a packet of information which includes instructions for activation of the award. The activation form as well as other important information about the grant can be found at https://proposalcentral.altum.com. Select the Award tab to see the Post Award Management Site.

Grant payments will be made separately by ACS and MRA. All payments are made to the sponsoring/lead institution and are mailed to the address indicated on the grant activation form. Continued funding throughout the grant period is contingent upon institution complying with all the terms related to the grant; and failure to comply with all the grant terms may result in a suspension of grant funding, or cancellation of the grant, to be determined by ACS and MRA in its sole discretion. Details regarding the payment schedule will be provided in the Notification of Award letter.

Personnel compensated in whole or in part with these funds are not considered employees of the ACS or MRA. Institutions are responsible for issuing the appropriate IRS tax filings for all individuals receiving compensation from these grants and are responsible for withholding and paying all required federal, state, and local payroll taxes about such compensation. Any tax consequences are the responsibility of the individual recipient and the sponsoring institution. We advise all grant and award recipients to consult a tax advisor regarding the status of their awards.

8. **ANNUAL AND FINAL PROGRESS REPORTS**

Annual and final reports represent a critical part of responsible stewardship of the donated dollars. We greatly appreciate your efforts to assist us in fulfilling this important commitment to our donors.

1. Both nontechnical and scientific progress reports are to be submitted each year within 60 days after the first and subsequent anniversaries of the start date of the grant, and final reports are due within sixty days after the grant has terminated. To access the necessary forms for annual and final progress reports, please go to https://proposalcentral.altum.com.

2. The final report should cover the entire grant period. In the event a grant has been extended without additional funds, the final report is not due until the official termination date of the grant. If the grant is terminated early, a final report must still be completed within 60 days of the termination date.

3. Reports are to be submitted in a timely manner. If this is not possible, a written request to extend the reporting deadline must be made.

4. Please note that up to date annual reports are required when requesting any grant modifications including transfers or no cost extensions.
9. **FINANCIAL RECORDS AND REPORTS**

A report of expenditures must be submitted within 90 days of the expiration date of the grant as indicated in the award letter. Any change in terms such as a no-cost extension will alter the date that the report is due. Annual financial reports are not required. To access the necessary forms, please go to https://proposalcentral.altum.com. Signatures of the principal investigator and the institution’s financial officer are required. Any unexpended funds must be returned to the Society.

Reports are to be submitted in a timely manner. If this is not possible, a written request to extend the reporting deadline must be made.

Institutions must maintain separate accounts for each grant, with substantiating invoices available for audit by representatives of the American Cancer Society. The Society is not responsible for expenditures made prior to the start date of the grant, costs incurred after termination or cancellation of the grant, or for commitments against a grant not paid within 60 days following the expiration date, or any expenditure that exceed the total amount of the award.

10. **EXPENDITURES**

Grants are not designed to cover the total cost of the research proposed nor the investigator’s entire compensation. The grantee's institution is expected to provide the required physical facilities and administrative services normally available at an institution.

For grants that allow indirect costs, the calculation of allowable indirect costs includes all budget items except permanent equipment. The Society's research grants do not provide funds (direct budget) for such items as:

- Secretarial/administrative salaries
- Student tuition and student fees including graduate and undergraduate; however, tuition is an allowable expense for the principal investigator of a Mentored Research Scholar Grant.
- Foreign travel (special consideration given for attendance at scientific meetings held in Canada)
- Books and periodicals except for required texts for coursework in the approved training plan for MRSGs.
- Membership dues
- Office and laboratory furniture
- Office equipment and supplies
- Rental of office or laboratory space
- Recruiting and relocation expenses
11. OWNERSHIP OF EQUIPMENT
Equipment purchased under research grants or extensions thereof is for the use of the principal investigator and collaborators. Title of such equipment shall be vested in the institution at which the principal investigator is conducting the research. In the event the American Cancer Society authorizes the transfer of a grant to another institution, equipment necessary for continuation of the research project purchased with the grant funds may be transferred to the new institution. Title to such equipment shall be vested in the new institution.

12. PUBLICATIONS AND OTHER RESEARCH COMMUNICATION
Publications resulting from research or training activities supported by the American Cancer Society and the Melanoma Research Alliance must contain the following acknowledgment: "Supported by (insert name of grant and number) from the American Cancer Society and the Melanoma Research Alliance." If there are multiple sources of support, the acknowledgment should read "Supported in part by (insert name of grant and number) from the American Cancer Society and the Melanoma Research Alliance" along with references to other funding sources. The funders support should also be acknowledged by the grantee and by the institution in all public communication of work resulting from this grant, including scientific abstracts (where permitted), posters at scientific meetings, press releases or other media communications, and Internet-based communications.

It is helpful if investigators notify their Program Directors when manuscripts have been accepted for future publication. This will allow ample time to consider and coordinate any additional public or Society-wide notifications.

ACS and MRA grants to you a limited, revocable, non-transferable license to use the ACS logo (as shown below) about your funded work. We encourage you to use the ACS and MRA logos on any scientific poster, in a Power Point presentation, or any other visual presentation about your funded work where the ACS and MRA are noted as a funding source. In turn you agree to provide any materials featuring the logos to ACS and MRA upon our request. Permission to use the logo is limited to the uses outlined in the above.

13. NOTIFICATION OF CHANGES
Applicants are not allowed to change the research project or team without prior approval from ACS. The PI should notify ACS immediately if there are any changes in team members or other research personnel or major barriers that impact the study timeline. Request to change the research proposal may not be accepted and may result in termination of the grant.

Change of Institutions: To transfer or change institutions during a grant period, please contact your program director to initiate the process.
Please note: annual reports are required prior to approval of any grant modifications including transfers and no cost extensions. The Society reserves the right to deny requests for extensions, transfers, or leave of absence.

14. ORGANIZATIONAL ASSURANCES:
The Principal Investigator and their Institution is responsible for ensuring that organizational assurances/certification are obtained. IRB and/or IACUC approvals, if applicable, are required before grant activation.

All activities involving human subjects or vertebrate animals must be approved by an appropriate institutional committee before the application will be funded. Furthermore, compliance with current US Department of Health and Human Services research subjects’ protection regulations and ACS guidelines for conflict of interest, recombinant DNA, and scientific misconduct is required. The assurances/certifications are made and verified by the signature of the institutional official signing the application.

The Institutional Official signing the application further certifies that the Institution will be accountable both for the appropriate use of any funds awarded and for the performance of the grant-supported project or activities resulting from this application. The Institution may be liable for the reimbursement of funds associated with any inappropriate or fraudulent conduct of the project activity.

For funded grants, it is the responsibility of the institution to immediately report to ACS any action including recertification or loss of IRB approval which may occur during the term of the award that is related to the work described in the grant application.

By accepting an award, you agree to the Guidelines for Maintaining Research and Peer Review Integrity that can be found in the appendix of these policies.

AMERICAN CANCER SOCIETY-MELANOMA RESEARCH ALLIANCE RESEARCH FOR PROPOSALS: UNDERSTANDING, PREVENTING AND MANAGING IMMUNOTHERAPY-RELATED ADVERSE EVENTS (irAEs) ASSOCIATED WITH CHECKPOINT INHIBITION FOR MELANOMA AND OTHER CANCERS

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A. GENERAL INFORMATION

1. ACCESSING THE ACS GRANT APPLICATION SYSTEM

Access the American Cancer Society Research site at www.cancer.org.
- Select “Explore Research” followed by “Apply for a Research Grant” > “Grant Types”.
- Select “ACS-MRA RFA: “Understanding, Preventing and Managing Immunotherapy-related Adverse Events (irAEs) Associated with Checkpoint Inhibition for Melanoma and Other Cancers.” You are now able to access the electronic grant application process at proposalCENTRAL.

- Once you reach proposalCENTRAL, follow their instructions to login/register and to complete and submit an application.
- The key steps for starting an application are as follows:
  Click on “Create New Proposal” to select a grant program and start your grant application. Locate the appropriate grant and click on “Apply Now” to create a proposal. Enter a Project Title (unless one is provided) and click SAVE. Once you have clicked on the “Save” button, the links to the other pages of the application appear in the Proposal Sections menu. Your saved application is stored under the “Manage Proposals” tab.

Please note: Detailed information is available through tutorials, provided on the proposalCENTRAL login page.

If you have problems accessing or using the electronic application process, click on “Help” or contact ALTUM Customer Service at pcsupport@altum.com or 1-800-875-2562.

2. FORMATTING THE APPLICATION

Applicants must adhere to the following instructions.
- Insert your name in the header for each section of the application
- Application documents may be single or double-sided.
- Type size: Use 12 point Times New Roman or 11-point Arial as the minimum font size for the text of the application. A 10-point Times New Roman or 9-point Arial font type may be used for figures, legends, and tables.
- Single-spaced text is acceptable, and space between paragraphs is recommended.
- Margins: The margins of your text should be at least 0.5 inches all around, unless a form with different margins is supplied in the Application Templates.
- Page numbering:
  Cover Pages- The first few pages of the application form are considered cover pages and are not numbered. The cover pages include the Signature Page, Contact Page, General Audience Summary and Structure Technical Abstract (if applicable).
Proposal Sections: The proposal sections are listed in the Table of Contents and must be numbered in the upper right hand corner. Each section should be numbered independently.

Appendix: The appendix is part of the electronic application

3. CHANGES TO THE APPLICATION

Withdrawal of application: Please advise the Society promptly, in writing (or email), should you decide to withdraw your application for any reason. Your letter (or email) to the Program Director identified in the application acknowledgment letter should include your name, the application number, and the reason for withdrawal. If you are withdrawing because you have accepted funding from another organization, please let us know who will be funding your work.

Change of address: Notify the Society in writing (email) of any changes of address, email or phone number, following the submission of an application. Include your name and the application number. We also recommend that you update your information in proposalCENTRAL.

Change of institution: If you are an applicant for an ACS grant and change your institution, contact the Program Director identified in the acknowledgment email, who will determine whether your application can be reviewed.

4. EXPLANATION OF REQUIRED INFORMATION

Title Page: Most of the information that is collected online at proposalCENTRAL appears on the cover pages.

Project Title: The title should not exceed 75 characters in length (including spaces). Do not use abbreviations unless necessary.

Principal Investigator/Applicant Information: Some (or all) of the required information will have been automatically filled in from your profile. The information was provided when you initially registered with proposalCENTRAL and completed the Professional Profile. If any of this information is not current at the time of submission, you will need to update the Professional Profile before finalizing this section and submitting the final version of your application. Pay attention to your contact information as all notifications to you will be sent using this information. Please keep contact information up to date.

Citizenship Status: An appropriate selection must be made in the Professional Profile. Indicate your current citizenship status. You must provide your country of citizenship. There are no citizenship restrictions.

Project Coding: Donors frequently have an interest in funding types of cancer research. Thus, Areas of Research (Common Scientific Outline –CSO) and Types of Cancer must be selected.
Space: If appropriate, indicate the approximate area of committed, independent research space provided by your institution to support your research program, as well as the name of the department chair responsible for verification of this research space. You must insert a value on the electronic form, even if you need to enter a 0 (zero).

Institutional Officials: In addition to the name and address of the official authorized to sign for the institution, include an address for mailing checks. Institutional officials should sign the front page. Original signatures are not required; electronic signatures are acceptable. Department Chair: Indicate name, department, and email address of the department chair. Department chairs should sign the front page to affirm the title of investigator and the committed resources.

Key Personnel: In addition to the Principal Investigator, Key Personnel (e.g. Collaborators) are defined as individuals who will contribute to the scientific development or execution of the project in a substantive, measurable way whether salaries are requested. Typically, these individuals have doctoral or professional degrees although individuals at the masters or baccalaureate level can be included if their contribution meets the above definition of Key Personnel.

5. GENERAL AUDIENCE SUMMARY

The general audience summary is a very important part of the application and is intended to provide a clear overview of the proposed research to people who are not trained in the sciences but who are interested in cancer research. These include stakeholders, ACS staff members, potential donors and the general public. Stakeholders are individuals without formal scientific or medical training who have a strong personal interest in the prevention and control of cancer. They are included as full voting members of all peer review panels. The Stakeholder evaluation of the general audience summary becomes an important part of the overall review of the application by the peer review committee since their primary focus is on how the proposed work will be of value to cancer patients and their families.

ACS staff members who work with major donors also use these summaries to identify projects appropriate to the interests of donors who wish to support specific areas of cancer research. Furthermore, summaries of all grants made by the Society are made available to the general public. ACS staff members with responsibility for communicating ACS research to local media may also use the summaries to describe the research funded in a particular region of the country.

The general audience summary must not duplicate the structured technical abstract. It should be written in a way that makes the project easily understood by the audience described above without scientific jargon. See the Samples of General Audience Summaries in the Appendix for examples of a properly constructed summary. This summary should describe the background to the research, the questions to be asked, and the information to be obtained. The use of symbols and Greek characters should be avoided for the general audience; if they must be used, they have to be spelled out since they will not appear as characters in the text.
This form is limited to 3,000 characters, including spaces and will truncate at that point. Characters in excess of the limit are not transmitted with the application resulting in an incomplete summary. **Failure to submit this correctly may result in the disqualification of your application.**

If this application is funded, this description will become public information. Therefore, do not include proprietary/confidential information.

**6. STRUCTURED TECHNICAL ABSTRACT**

The structured technical abstract is a clear and concise summary of the proposed research or scholarly project for general scientific audiences.

Please use the outline below. See the Appendix for an example of a structured technical abstract.

- **Background**: Provide a brief statement of the ideas and reasoning behind the proposed work.
- **Objective/hypothesis**: State the objective/hypothesis to be tested. Cite evidence or provide a rationale that supports it.
- **Specific aims**: Concisely state the specific aims of the study.
- **Study design**: Briefly describe the study design, emphasizing those elements you consider most relevant to assignment of the proposal for peer review.
- **Anticipated Impact**: If aims are achieved what will be the anticipated impact of your research results and how will the findings be used inform future research and/or advance the science.

This form is limited to 3,000 characters, including spaces and will truncate at that point. Characters in excess of the limit are not transmitted with the application resulting in an incomplete summary. Please submit a complete Structured Technical Abstract within the character limit. **Failure to submit this correctly may result in the disqualification of your application.**

**7. PROJECT CODING**

**Please note: Red asterisks indicate required fields.**

Donors frequently have an interest in funding particular types of cancer research. Thus, Areas of Research (Common Scientific Outline –CSO) and Types of Cancer must be selected for these summaries to be presented to donors for special funding opportunities. See the Areas of Research in the Appendix for filling out the forms. Please note that in completing the Areas of Research section, appropriate items may also include those listed under Resources and Infrastructure Related to [specific area]. See the Appendix for specific terms and examples.
The information requested is not part of the application used by the Peer Review Committee for scientific review, and should not be submitted with your paper copy. However, the information is important and assists the Society in communication to the public about its portfolio of applications and grants.

8. ASSURANCES AND CERTIFICATION

All activities involving human subjects or vertebrate animals must be approved by an appropriate institutional committee before the application will be funded by the American Cancer Society. Furthermore, compliance with current US Department of Health and Human Services and ACS guidelines for conflict of interest, recombinant DNA, and scientific misconduct is required. The assurances/certifications are made and verified by the signature of the institutional official signing the application.

Vertebrate animals. Every proposed research project involving vertebrate animals must be approved by an appropriate Institutional Animal Care and Use Committee (IACUC), in accordance with Public Health Service Policy on Humane Care and Use of Laboratory Animals, before the application will be funded by the American Cancer Society. Enter the date of the most recent IACUC approval in the space provided.

All research supported by the American Cancer Society (including subcontracted activities) involving vertebrate animals must be conducted at performance sites which are covered under an approved Animal Welfare Assurance. **It is the responsibility of the institution to immediately report to ACS any action including recertification or loss of IACUC approval which may occur during the term of any award that is pertinent to the work described in the grant application.**

Human Subjects. All proposed research projects involving human subjects must be approved by the appropriate Institutional Review Board (IRB).

The institution must have received approval from the Office for Human Research Protections (OHRP) of the US Department of Health and Human Services (DHHS). Enter the institution's Assurance of Compliance number(s) in the space provided. Copies of the DHHS policy and information regarding the assured status and assurance numbers of institutions may be obtained from OHRP. The definitions and further sources of clarification for all of these assurances are found in the NIH Grants Policy Statement (Revised 12/03), www.grants.nih.gov/grants/policy, or the NIH Office of Extramural Research.

If institutional review of human subjects (IRB certification) or vertebrate animal use (IACUC certification) has not been completed before the submission date of the application, you must indicate that the approval is pending on the certification page and give the appropriate institutional reference numbers if available. **Certification of the institutional committee review, clearly labeled with the assigned American Cancer Society application number, must be received prior to activation of a grant for funding. Failure to supply the American Cancer Society with completed IRB**
and/or IACUC certifications prior to the approved start of funding will result in withholding of payments and may result in cancellation of funding.

Please note: applications for the Institutional Research Grant and certain Health Professional Training Grants do not require submission of IRB and IACUC certifications. Institutions must, however, be in compliance with the requirements noted above in order to use American Cancer Society grant funding for activities involving human subjects or vertebrate animals.

For funded grants, it is the responsibility of the institution to immediately report to ACS any action including recertification or loss of IRB approval which may occur during the term of the award that is related to the work described in the grant application.

9. APPLICATION SUBMISSION AND REQUIRED SIGNATURES

Applications must be submitted in two formats: an electronic version and one paper copy.

**A. SUBMISSION OF ELECTRONIC APPLICATION**

- **All application attachments including the appendix must be uploaded as .pdf documents.** See proposalCENTRAL FAQ or contact support at 1-800-875-2562 if you need assistance.
- **Validate the application on proposalCENTRAL.** This is an essential step. An application that has not been validated cannot be submitted.
- **Print application via proposalCENTRAL.** To do so, choose “Print” on the menu and select “Print Signature Pages and Attached PDF Files”. **Do not print cover pages for an application that has not been validated.**
- Please collect all required signatures on the paper copy before submitting. Original signatures are not required; electronic signatures are acceptable. Please note, you do not upload the signed copy of the front page.; it is to be submitted with the paper copy.
- If any modifications were made during the signature process, make certain that all sections of the electronic version are revised to match the paper copy that is being submitted.
- If you have technical questions regarding the electronic application process, feel free to contact Altum at pcsupport@altum.com or 1-800-875-2562.
- **Submission of the electronic version of application should be done after your institution has prepared the application for mailing.** You have until 5:00 PM Eastern time on the deadline date to complete the electronic submission. Note that the appendix materials are now submitted electronically. Paper copies will no longer be provided to reviewers so any appendix materials must be uploaded to proposalCENTRAL to be considered during the review process.
- **The electronic applications must be submitted at the proposalCENTRAL website by close of business (5:00 PM EST) on the specified deadline date.** For the
convenience of the applicant, a paper copy is due one day after submission of the electronic copy. If the deadline falls on a weekend or holiday, applications will be accepted the following business day.

Please note: You will not be able to make any changes to the forms or upload any modifications to the files after submission.

B. ASSEMBLY AND SUBMISSION OF PAPER COPY

The paper copy of the application must carry the signatures (front page) and contact information (second page) for
- The Applicant
- The Institutional Signing Official
- The Department Head

See program specific instructions for additional required signatures.

A single paper copy of the application must be received by the American Cancer Society Corporate Center no later than 5:00 PM Eastern time on the next business day following the deadline date for the electronic submission.

The paper copy must be assembled as described below. To reduce the chance of losing an application, we urge institutions to mail only one application per package. If more than one application is included in a package, provide a bright-colored cover sheet listing the applications enclosed and stating in ½ inch or larger lettering "MULTIPLE APPLICATIONS ENCLOSED."

The application should be held together with a rubber band or binder clips. Please do not staple. Send the complete application package to:

The American Cancer Society
Extramural Research Department
250 Williams Street NW, 6th Floor
Atlanta, GA 30303-1002
404-329-7558

B. PREPARING THE APPLICATION

1. APPLICATION TEMPLATES

An application consists of several sections that must be uploaded before the online application is submitted. Templates for these sections are available once an application is started on proposalCENTRAL. The templates must be downloaded and completed offline. Click the download link to save templated to your computer. Completed
templated must be converted into PDF documents before uploading to corresponding sections. Detailed below are the instructions for completing the individual sections.

2. TABLE OF CONTENTS (PAGE 1.1)

Complete the Table of Contents by indicating the appropriate page numbers for the Research Plan section; limit the length of the Table of Contents to two pages.

3. BIOGRAPHICAL SKETCH OF APPLICANT (PAGE 2.1)

Complete the NIH Biosketch template. Follow the formats and instructions provided the NIH.

4. RESEARCH PLAN AND ENVIRONMENT (PAGE 3.1)

Section A below (Specific Aims) should not exceed 1 page. Sections B-F below must not exceed 5 pages. This page limit does not include Experimental Details (G) Environment (H), the Statement of Science Outreach and Advocacy (I), or the References (J).

Follow the format for Sections A-I (listed above) on the provided template. Proposals should be realistic in terms of work to be accomplished in the proposed project for which support is requested. Failure to conform to the guidelines on type size, page length, or project scope may result in the application being returned to the investigator without review.

A. Hypothesis and Specific Aims. List the hypotheses, objectives, and goals of the research proposed and describe the specific aims briefly. In addition, state the anticipated impact of the research on the prevention, early detection, reduction and/or management of life-altering and/or outcome-limiting side-effects

B. Background and Significance. Concisely summarize and critically evaluate related work done by others. Specifically state how the successful completion of the work proposed in the specific aims will advance scientific knowledge or aspects of clinical practice that are important for a better understanding of immune related adverse events (irAEs) or management of cancer patients being treated with checkpoint immunotherapies. The critique of the literature should also include pertinent evidence-based interventions that inform your approach and should address critical gaps in knowledge. Additionally, the model(s) that underpins the research approach and forms the basis of your conceptual framework should be summarized here. If aims are realized, how will the results of this study impact cancer patients, clinical practice and/or policy?

C. Statement of Cancer Relevance (max 250 words). What is the cancer relevance and importance to the targeted area on the field of cancer research related to irAEs? This section of the application is important to the Stakeholders (non-scientific members) on the Peer Review Committees and to several general audiences,
including donors. The use of technical terminology or scientific jargon should therefore be avoided. Describe the short-term and long-term contributions the project is designed to make to the prevention and management of cancer survivors being treated with checkpoint immune inhibitors. Outline the expected contribution of the study to controlling the overall cancer burden. This description might include: an estimate of the potential patient target population; anticipated effects on morbidity and/or mortality; possible impact on quality of life; and the extent to which the findings may be applicable beyond the specific aspect of cancer to be investigated. This section should not exceed 250 words.

D. Innovation. Provide a rationale for why this proposed research is novel/innovative in ways that challenge and/or seek to shift current research understanding or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions. Describe how the research proposes meaningful improvements or address critical gaps. Describe how the research question was developed and for team awards how insight from team members of various disciplines members were utilized to create study aims, research design and methods.

1. Explain how the application challenges and seeks to shift current research or paradigms.
2. Describe any novel theoretical concepts, approaches or methodologies, instrumentation or intervention(s) to be developed or used, and any advantage over existing methodologies, instrumentation or intervention(s).
3. Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation or interventions.

E. Preliminary Studies and Previous Experience. Provide results of research accomplished by you that are relevant to this proposal in a sufficiently comprehensive manner to indicate their significance. For existing teams, provide a succinct summary of the previous work including specific accomplishments pertinent to the proposed scope of work. If the partnership is new, describe how the collective assets of both partners will facilitate the success of this study and provide the foundation for future collaboration.

Reprints or preprints may serve in lieu of a detailed report and should be included in the appendix. Reprints and preprints should be included in each appendix set. Note that the entire application is considered confidential, including reports of unpublished research.

F. Research Design and Methods. State the study design and describe your proposed implementation methods in sufficient detail to permit evaluation by other scientists. Describe the plan for data collection and analysis and discuss potential difficulties and limitations of the methods and procedures, and provide alternative approaches. Order your priorities, and estimate the length of time that you believe will be required to complete each specific aim. Although the time estimated should
not exceed the term for which support is requested, it is helpful to state how this project fits in with your long-term research goals.

G. Experimental Details (not to exceed 3 pages).
   Details:
   Timeline: Provide a timeline with milestones for the project period

   Potential for Knowledge transfer: Clearly defined plan of how the results of the study will be used to develop future research and its practical clinical benefit.

H. Environment. Describe briefly the space and equipment available for you to carry out the proposed research project. Investigators must have an institutional commitment of research facilities. The amount of committed space must be verified by the Department Chair (signature required on title cover of the application). This section is of major importance for applicants whose appointment is not in the tenure stream.

I. Statement of Science Outreach and Advocacy (not to exceed one page): The ACS considers it important that scientists communicate the results of their research to a wide range of communities. Explain the potential impact of your proposed project on your community, and to the American Cancer Society’s mission of eliminating cancer as a major health problem. Share any previous experiences in science outreach and advocacy. Describe your future for disseminating your work in the cancer arena through advocacy, awareness, education, or service. Please include your plans for sharing your research and research findings with your (non-academic) community members and for engaging with community partners in the dissemination process.

J. References. The list of references should correspond to the citations under headings A-D above. Each literature citation should include the names of all authors, title, book or journal, volume number, page numbers, and year of publication. There is no page limitation for the list of references and this section is not included in the 5-page limit for Pilot awards (Sections B-F).

5. **DETAILED BUDGET (PAGE 4.1)**

   A. Personnel.
   Names and positions of all key personnel must be individually listed and the percentage of time to be devoted to the project by each person should be noted, even when salary is not requested. List all collaborators (defined as individuals who will participate actively in the design and/or execution of the studies). Details of contractual arrangements with collaborators should be provided in the Justification of Budget section of the application.

   If the individual has not been selected, please list as “vacancy.” Personnel may receive salary support up to a maximum that equals the National Cancer Institute salary cap, prorated per their percent effort on the project.
The costs to the institution of employee fringe benefits should be indicated as a percent of the employee's salary. The amount of fringe benefits requested must be prorated to the salary requested. (For example, if 50 percent of an individual's annual salary is requested then no more than 50 percent of that individual's annual cost for fringe benefits can be requested.)

**Please Note:** Consultants are not considered key personnel, but rather are defined as individuals who will provide any combination of advice, guidance, and reagents but do not commit any specified measurable effort (i.e., person months) to the project and should be included in the budget as subcontractors.

**B. Equipment.**

**Permanent equipment** - Defined as items of nonexpendable property with a purchase cost per unit that equals or exceeds $5,000 with a useful life of more than one year. List separately and justify the need for each item of permanent equipment. Note: the cost of permanent equipment is not included in the Direct Cost total used to calculate Indirect Costs.

**Small or expendable equipment** – Defined as expendable property with a purchase cost per unit that is less than $5,000 and/or that has a short service life (<1 year). Note: the cost of small or expendable equipment may be included in the Direct Cost total used to calculate Indirect Costs.

**General purpose equipment** – Equipment such as computers or laptops used primarily or exclusively in the actual conduct of the proposed scientific project are considered direct cost and may be included in the Direct Cost total used to calculate Indirect Costs. Computers, laptops or other general purpose equipment that will be used on multiple projects or for personal use should not be listed as a direct cost, and should not be included in the calculation for indirect cost.

**C. Supplies.** Group into major categories (glassware, chemicals, radioisotopes, survey materials, animals).

**D. Travel.** Travel funds are restricted for domestic travel within the US, its territories and Canada only.

**E. Miscellaneous Expenditures.** List specific amounts for each item; examples of expenditures allowed include: publication costs, special fees (e.g., publication costs, pathology, computer time and scientific software, and equipment maintenance).
F. **Subcontracts.** If any portion of the proposed research is to be carried out at another institution, enter the total costs and provide a categorical breakdown of costs using duplicate copies of the grant application Budget and Justification of Budget pages. Subcontracts required to complete the research project may be with public or private institutions provided they are not in violation of ACS policies. Subcontracts involving a contractor residing outside the borders of the United States are not permitted unless the applicant can document that it is not feasible to have the work performed within the United States; and use of any subcontractor outside of the United States must be approved in writing by ACS prior to the performance of any work funded by the ACS grant.

**Administrative pages:** A Letter of Agreement pertaining to the subcontract should be included in the Appendix

G. **Indirect Costs:** indirect costs, overhead costs or other institutional levies will not be paid by either MRA or ACS. Fringe benefits for personnel salaries are allowable.

H. **Total Amount Requested.** Budget totals should reflect a maximum duration of 2 years. Enter the sum of all years of requested direct costs and round to the nearest thousand dollars.

6. **JUSTIFICATION OF BUDGET**

Justify the need for personnel, supplies, travel, miscellaneous items and all items of permanent equipment costing over $5,000. If the budget includes a request for funds to be expended outside the United States, its territories, or the Commonwealth of Puerto Rico, this section should include an explanation of why such costs are essential for the successful conduct of the project, and why there are no alternatives.

7. **BIOGRAPHICAL INFORMATION OF KEY PERSONNEL (PAGE 5.1)**

Complete the NIH Biosketch template. NOTE: Follow the formats and instructions provided by the NIH.

8. **OTHER SUPPORT (PAGE 6.1)**

Projects supported all or in part by another agency are not allowed for submission; this means that projects are considered to overlap if there are any shared Specific Aims or areas of budgetary overlap. The Peer Review Committees will make the final decision regarding any questions of overlap. The only exceptions are: (a) funds provided by the institution as “start-up” support to develop a new laboratory or to gather pilot data, and (b) awards that provide only salary support for the Principal Investigator. In the latter case, if the salary support for the PI's contribution to the project is covered by the other agency, no additional salary support for the PI may be requested in this grant application.
The following information is required for (1) the principal investigator and (2) all other professional persons listed on the budget page (including collaborators and subcontractors who will receive salary, but excluding consultants, postdoctoral fellows, technicians, and students). Please provide this information for each person separately and in the following manner. Use continuation pages if necessary.

**a. Current Support:** List all current awards including funding from intramural and extramural sources (e.g., institutional awards, and grants from for-profit, and not-for-profit agencies, including other grants from the American Cancer Society). For each award provide: (a) Source of funds—identify the agency, institute, foundation, or other organization that is providing the support. Include institutional, federal, public and private sources of support; (b) Grant number; (c) Title of project; (d) Dates of Approved/Proposed Project: Indicate the inclusive dates of the project as approved/proposed. For example, in the case of NIH support, provide the dates of the approved/proposed competitive segment; (e) Total Direct Costs; (f) Percent Effort/Person Months: For an active project, provide the level of actual effort in person months (even if unsalaried) for the current budget period. Person months should be classified as academic, calendar and/or summer; (g) Outline the goals of the project in a brief paragraph; and (h) Clearly indicate whether there is any overlap between this grant and the proposed study. If necessary, an explanatory letter may be included in the appendix to clarify the differences between the present application to the American Cancer Society and currently funded projects.

**b. Pending Support:** List all pending applications to other funding sources including funding from intramural and extramural sources (e.g., institutional awards, and grants from for-profit, and not-for-profit agencies, including other grants from the American Cancer Society). For each award provide: (a) Source of funds—identify the agency, institute, foundation, or other organization that is providing the support. Include institutional, federal, public and private sources of support; (b) Title of project; (c) Dates of Proposed Project: Indicate the inclusive dates of the project as approved/proposed. For example, in the case of NIH support, provide the dates of the approved/proposed competitive segment; (d) Total Direct Costs; (e) Percent Effort/Person Months. For a pending project, indicate the level of effort in person months as proposed for the initial budget period. In cases where an individual’s appointment is divided into academic and summer segments, indicate the proportion of each devoted to the project; (f) Outline the goals of the project in a brief paragraph. (g) Clearly indicate whether there is any overlap between this grant and the proposed study. If necessary, an explanatory letter may be included in the appendix to clarify the differences between the present application to the American Cancer Society and currently funded projects. In such cases, only one award can be accepted if both are approved for funding. The American Cancer Society does not negotiate partial funding of grants with overlapping specific aims.
c. Institutional Support (The following information is required for the principal investigator only): A statement from the Department Chair summarizing the institutional commitment and resources available to the support the Lead PI and proposed research, this may include: (a) a description of any “start-up” funds provided by the Institution to the applicant; (b) details of the Institutional commitment to the support of the applicant’s salary; and (c) the current term of the applicant’s appointment. These details should be confirmed in the Statement of Institutional Support from the Department Chair included in Section 13, below. Please note that the award of “start-up” funds does not decrease the chances of obtaining support; instead, such support is frequently considered by the Peer Review Committees as important evidence for institutional commitment to the research project.

Please keep the Scientific Program Director current on the status of all pending applications.

9. LIST OF LETTERS OF SUPPORT FROM COLLABORATORS/CONSULTANTS (PAGE 7.1)

Provide a list of collaborators/consultants. Then directly upload the letter from each individual collaborator/consultant. The letter should outline the role that person will play with sufficient detail for evaluation of the value of the individual contribution. You are not required to use the template.

10. COMPLIANCE STATEMENTS (PAGE 8.1-8.2)

Human Subjects:
Selection of study population: When conducting research on humans, provide the rationale for selection of your target population including the involvement of children, minorities, special vulnerable populations, such as, neonates, pregnant women, prisoners, institutionalized individuals, or others who may be considered vulnerable populations*. This should include research subject gender and the rationale for why certain populations may be excluded based on your research question and specific aims. Complete the planned enrollment form based on your proposed study sample size to estimate the total number of subjects by primary ethnicity and race, race/ethnicity subgroup (if applicable) and gender. For research involving human subjects estimate the planned enrollment based on your sample size calculations. Also, include estimates of the sample distribution by gender and race and ethnicity (if available). For example, if your sample size is 200, to complete the total number of subjects’ column by race (based on what you know about the population demographics or the existing dataset you plan to analyze) multiple by the estimated percentage.

<table>
<thead>
<tr>
<th>Estimated percentage of the population by race</th>
<th>Estimated Total number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% White</td>
<td>100 (200 x 0.50)</td>
</tr>
<tr>
<td>49 % AA</td>
<td>98 (200 x 0.49)</td>
</tr>
<tr>
<td>1 % Asian</td>
<td>2 (200 x 0.01)</td>
</tr>
</tbody>
</table>
For Applicants performing non-human subjects’ research please check the box that most appropriately describes your research.

**Potential benefits and risks and knowledge gained:** Succinctly describe the potential benefits and risks to subjects (physical, psychological, financial, legal, or other). Additionally, provide justification for why potential risks to subjects are reasonable in relation to the anticipated benefits to research participants and others. Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

**Research Specimens and Data:** If the proposed research involves bio-specimens, provide a description of how the research material will be obtained from living subjects and what materials will be collected. Additionally, describe the specific non-biological data from human subjects and how it will be collected, managed and protected (e.g. demographic data elements), including who will have access to research data and what measures will be implemented to keep personally identifiable private information confidential.

**Collaborating sites:** List any collaborating sites where research on human subjects will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

**Note:** See the Department of Health and Human Services Office of Research Protection Subparts B-D for additional protections for vulnerable populations.
http://www.hhs.gov/ohrp/policy/populations/index.html

**Vertebrate Animals.**
Provide rationale for inclusion of live vertebrate animals per the 1) necessity for the use of the animals and species proposed; 2) appropriateness of the strains, ages, and gender of the animals to be used for the experimental plan proposed; and 3) justifications for, and appropriateness of, the numbers used for the experimental plan proposed. When completing the Targeted Enrollment, Table select non-human subjects’ research and check the box that most appropriately describes your research.

**Biohazards**
Briefly describe whether materials or procedures proposed are potentially hazardous to research personnel, equipment, and/or the environment, and describe what protections will be used to mitigate any risk. The assessment related to biohazards should include potential biological or chemical hazards.

**Authentication of Key Biological and/or Chemical Resources**
Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.
Key biological and/or chemical resources may or may not be generated with ACS funds and:

1) may differ from laboratory to laboratory or over time;
2) may have qualities and/or qualifications that could influence the research data; and
3) are integral to the proposed research.

These include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics. Researchers should transparently report on what they have done to authenticate key resources, so that consensus can emerge.

Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals. Reviewers will assess the information provided in this Section. Any reviewer questions associated with key biological and/or chemical resource authentication will need to be addressed prior to award.

Information in this section must focus only on authentication and/or validation of key resources to be used in the study; all other methods and preliminary data must be included within the page limits of the research strategy. Applications identified as non-compliant with this limitation may be withdrawn from the review process.

11. STATEMENT OF INSTITUTIONAL SUPPORT (PAGE 9.1)

A letter from the Department Chair (or equivalent) must be included in the application. This letter should clearly indicate the commitment of the institution to the support of the applicant and their research program. Details should include, but are not limited to, salary support, dedicated space for the research proposal, startup funds and the amount of protected time for clinical researchers. The letter should also describe the Department’s long-term goals for the applicant’s career.

12. APPENDIX TO APPLICATION

In addition to the application templates, other key documents may be uploaded and submitted as part of the application. However, applicants are urged to keep this section as brief as possible.

Appended materials may include:
- Letter from ACS Eligibility Committee confirming eligibility (if applicable)
- Letters of support
- Recent reprints or preprints (optional)
- Clinical Protocols (if applicable)
- Logic Model (for dissemination and implementation pilots – if applicable)

It is not necessary to number the pages of the appendix, but please list by categories (i.e., reprints, preprints, etc.) in the Table of Contents of the application.
APPENDIX A: CLASSIFICATION CATEGORIES - AREAS OF RESEARCH

The areas of research are based on seven broad categories called the Common Scientific Outline (CSO) developed by the International Cancer Research Partnership (ICRP):

1. Biology
2. Etiology
3. Prevention
4. Early Detection, Diagnosis and Prognosis
5. Treatment
6. Cancer Control, Survivorship and Outcomes Research

Applicants are asked to select from the following codes:

1 – BIOLOGY

Research included in this category looks at the biology of how cancer starts and progresses as well as normal biology relevant to these processes.

1.1 Normal Functioning

Examples of science that would fit:
- Developmental biology (from conception to adulthood) and the biology of aging
- Normal functioning of genes, including their identification and expression, and the normal function of gene products, such as hormones and growth factors
- Normal formation of the extracellular matrix
- Normal cell-to-cell interactions
- Normal functioning of apoptotic pathways
- Characterization of pluripotent progenitor cells (e.g., normal stem cells)

1.2 Cancer Initiation: Alterations in Chromosomes

Examples of science that would fit:
- Abnormal chromosome number
- Aberration in chromosomes and genes (e.g., in chronic myelogenous leukemia)
- Damage to chromosomes and mutation in genes
- Failures in DNA repair
- Aberrant gene expression
- Epigenetics
- Genes and proteins involved in aberrant cell cycles
1.3 Cancer Initiation: Oncogenes and Tumor Suppressor Genes

Examples of science that would fit:

- Genes and signals involved in growth stimulation or repression, including oncogenes (Ras, etc.), and tumor suppressor genes (p53, etc.)
- Effects of hormones and growth factors and their receptors such as estrogens, androgens, TGF-beta, GM-CSF, etc.
- Research into the biology of stem cell tumour initiation

1.4 Cancer Progression and Metastasis

Examples of science that would fit:

- Latency, promotion, and regression
- Expansion of malignant cells
- Interaction of malignant cells with the immune system or extracellular matrix
- Cell mobility, including detachment, motility, and migration in the circulation
- Invasion
- Malignant cells in the circulation, including penetration of the vascular system and extrasavation
- Systemic and cellular effects of malignancy
- Tumor angiogenesis and growth of metastases
- Role of hormone or growth factor dependence/independence in cancer progression
- Research into cancer stem cells supporting or maintaining cancer progression

1.5 Resources and Infrastructure

Examples of science that would fit:

- Informatics and informatics networks
- Specimen resources
- Epidemiological resources pertaining to biology
- Reagents, chemical standards
- Development and characterization of new model systems for biology, distribution of models to scientific community or research into novel ways of applying model systems, including but not limited to computer-simulation systems, software development, in vitro/cell culture models, organ/tissue models or animal model systems. Guidance note: this should only be used where the focus of the award is creating a model. If it is only a tool or a methodology, code to the research instead.
- Education and training of investigators at all levels (including clinicians and other health professionals), such as participation in training workshops, conferences,
advanced research technique courses, and Master's course attendance. This does not include longer-term research-based training, such as Ph.D. or postdoctoral fellowships.

2 – ETIOLOGY

Research included in this category aims to identify the causes or origins of cancer - genetic, environmental, and lifestyle, and the interactions between these factors.

2.1 Exogenous Factors in the Origin and Cause of Cancer

*Examples of science that would fit:*

- Research into the role of lifestyle factors such as smoking, chewing tobacco, alcohol consumption, parity, diet, sunbathing, and exercise in the origin and cause of cancer or increasing the risk of cancer
- Research into the social determinants of cancer such as crime, housing dilapidation, neighbourhood level socioeconomic status and services and their relationship to cancer incidence and mortality etc.
- Studies on the effect(s) of nutrients or nutritional status on cancer incidence
- Development, characterization, validation, and use of dietary/nutritional assessment instruments in epidemiological studies and to evaluate cancer risk
- Environmental and occupational exposures such as radiation, second-hand smoke, radon, asbestos, organic vapors, pesticides, and other chemical or physical agents
- Infectious agents associated with cancer etiology, including viruses (Human Papilloma Virus-HPV, etc.) and bacteria (helicobacter pylori, etc.)
- Viral oncogenes and viral regulatory genes associated with cancer causation
- Contextual Factors Contributing to Cancer Incidence (e.g., race/ethnicity, socioeconomic status, neighborhood factors, community factors, built environment).

2.2 Endogenous Factors in the Origin and Cause of Cancer

*Examples of science that would fit:*

- Free radicals such as superoxide and hydroxide radicals
- Identification /confirmation of genes suspected of being mechanistically involved in familial cancer syndromes; for example, BRCA1, Ataxia Telangiectasia, and APC
• Identification/confirmation of genes suspected or known to be involved in "sporadic" cancer events; for example, polymorphisms and/or mutations that may affect carcinogen metabolism (e.g., CYP, NAT, glutathione transferase, etc.)
• Investigating a role for stem cells in the etiology of tumours

2.3 Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors

Examples of science that would fit:

• Gene-environment interactions
• Interactions of genes with lifestyle factors, environmental, and/or occupational exposures such as variations in carcinogen metabolism associated with genetic polymorphisms
• Interactions of genes and endogenous factors such as DNA repair deficiencies and endogenous DNA damaging agents such as oxygen radicals or exogenous radiation exposure

2.4 Resources and Infrastructure Related to Etiology

Examples of science that would fit:

• Informatics and informatics networks; for example, patient databanks
• Specimen resources (serum, tissue, etc.)
• Reagents and chemical standards
• Epidemiological resources pertaining to etiology
• Statistical methodology or biostatistical methods
• Centers, consortia, and/or networks
• Development, characterization and validation of new model systems for etiology, distribution of models to the scientific community or research into novel ways of applying model systems, including but not limited to computer-simulation systems, software development, in vitro/cell culture models, organ/tissue models or animal model systems. Guidance note: this should only be used where the focus of the award is creating a model. If it is only a tool or a methodology, code to the research instead.
• Education and training of investigators at all levels (including clinicians and other health professionals), such as participation in training workshops, conferences, advanced research technique courses, and Master's course attendance. This does not include longer term research based training, such as Ph.D. or post-doctoral fellowships.
3 – PREVENTION

Research included in this category looks at identifying individual and population-based primary prevention interventions, which reduce cancer risk by reducing exposure to cancer risks and increasing protective factors.

3.1 Interventions to Prevent Cancer: Personal Behaviors (Non-Dietary) that Affect Cancer Risk

Examples of science that would fit:

- Research on determinants of personal behaviors, such as physical activity, sun exposure, and tobacco use, known to affect cancer risk and interventions (including educational and behavioral interventions directed at individuals as well as population-based interventions including social marketing campaigns, environmental supports, and regulatory, policy and legislative changes) to change determinants
- Directed education to specified populations of patients, health care providers, and at-risk groups about cancer risk and prevention and relevant interventions with the intent of promoting increased awareness and behavioral change. This includes communication of lifestyle models that reduce cancer risk, such as communicating smoking and tobacco cessation interventions

3.2 Dietary Interventions to Reduce Cancer Risk and Nutritional Science in Cancer Prevention

Examples of science that would fit:

- Quantification of nutrients, micronutrients, and purified nutritional compounds in cancer prevention studies
- Development, characterization, validation, and use of dietary/nutritional assessment instruments to evaluate cancer prevention interventions
- Research on determinants of dietary behavior and interventions to change diet (including educational and behavioral interventions directed at individuals as well as population-based interventions including social marketing campaigns, environmental supports, and regulatory and legislative changes) to change diet
- Education of patients, health care providers, at-risk populations, and the general population about cancer risk and diet
- Communicating cancer risk of diet to underserved populations, at-risk populations, and the general public
- Communication of nutritional interventions that reduce cancer risk

3.3 Chemoprevention

*Examples of science that would fit:*

- Chemopreventive agents and their discovery, mechanism of action, development, testing in model systems, and clinical testing

3.4 Vaccines

*Examples of science that would fit:*

- Vaccines for prevention, their discovery, mechanism of action, development, testing in model systems, and clinical testing (e.g., HPV vaccines)
- Guidance note: only preventive/prophylactic vaccine research should be included here. Vaccines for the treatment of cancer should be coded to 5.3 or 5.4, depending on the phase of development.

3.5 Complementary and Alternative Prevention Approaches

*Examples of science that would fit:*

- Discovery, development, and testing of complementary/alternative medicine (CAM) approaches or other primary prevention interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses
- Mind and body medicine (e.g., meditation, acupuncture, hypnotherapy), manipulative and body-based practices (e.g., spinal manipulation, massage therapy), and other practices (e.g., light therapy, traditional healing) used as a preventive measure.

3.6 Resources and Infrastructure Related to Prevention

*Examples of science that would fit:*

- Informatics and informatics networks; for example, patient databanks
- Specimen resources (serum, tissue, etc.)
- Epidemiological resources pertaining to prevention
- Clinical trials infrastructure
- Statistical methodology or biostatistical methods
- Centers, consortia, and/or networks
• Development and characterization of new model systems for prevention, distribution of models to scientific community or research into novel ways of applying model systems, including but not limited to computer-simulation systems, software development, in vitro/cell culture models, organ/tissue models or animal model systems. Guidance note: this should only be used where the focus of the award is creating a model. If it is only a tool or a methodology, code to the research instead.

• Education and training of investigators at all levels (including clinicians and other health professionals), such as participation in training workshops, conferences, advanced research technique courses, and Master's course attendance. This does not include longer term research based training, such as Ph.D. or post-doctoral fellowships.

### 4 – EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Research included in this category focuses on identifying and testing cancer markers and imaging methods that are helpful in detecting and/or diagnosing cancer as well as predicting the outcome or chance of recurrence or to support treatment decision making in stratified/personalised medicine.

#### 4.1 Technology Development and/or Marker Discovery

*Examples of science that would fit:*

• Discovery or identification and characterization of markers (e.g., proteins, genes, epigenetic), and/or technologies (such as fluorescence, nanotechnology, etc.) that are potential candidates for use in cancer detection, staging, diagnosis, and/or prognosis

• Use of proteomics, genomics, expression assays, or other technologies in the discovery or identification of markers

• Defining molecular signatures of cancer cells, including cancer stem cells (e.g., for the purposes of diagnosis/prognosis and to enable treatment decision planning in personalized/stratified/precision medicine)

#### 4.2 Technology and/or Marker Evaluation With Respect to Fundamental Parameters of Method

*Examples of science that would fit:*
• Development, refinement, and preliminary evaluation (e.g., animal trials, preclinical, and Phase I human trials) of identified markers or technologies such as genetic/protein biomarkers (prospective or retrospective) or imaging methods (optical probes, PET, MRI, etc.)
• Preliminary evaluation with respect to laboratory sensitivity, laboratory specificity, reproducibility, and accuracy
• Retrospective studies of existing sample collections and evaluation of markers in ancillary studies
• Research into mechanisms assessing tumor response to therapy at a molecular or cellular level

4.3 Technology and/or Marker Testing in a Clinical Setting

Examples of science that would fit:

• Evaluation of clinical sensitivity, clinical specificity, and predictive value (Phase II or III clinical trials)
• Quality assurance and quality control
• Inter- and intra-laboratory reproducibility
• Testing of the method with respect to effects on morbidity and/or mortality
• Study of screening methods, including compliance, acceptability to potential screenees, and receiver-operator characteristics. Includes education, communication, behavioral and complementary/alternative approaches to improve compliance, acceptability or to reduce anxiety/discomfort.
• Research into improvements in techniques to assess clinical response to therapy

4.4 Resources and Infrastructure Related to Detection, Diagnosis, or Prognosis

Examples of science that would fit:

• Informatics and informatics networks; for example, patient databanks
• Specimen resources (serum, tissue, images, etc.)
• Clinical trials infrastructure
• Epidemiological resources pertaining to risk assessment, detection, diagnosis, or prognosis
• Statistical methodology or biostatistical methods
• Centers, consortia, and/or networks
• Development, characterization and validation of new model systems for detection, diagnosis or prognosis, distribution of models to the scientific community or research into novel ways of applying model systems, including but not limited to computer-simulation systems, software development, in vitro/cell
culture models, organ/tissue models or animal model systems. Guidance note: this should only be used where the focus of the award is creating a model. If it is only a tool or a methodology, code to the research instead.

- Education and training of investigators at all levels (including clinicians and other health professionals), such as participation in training workshops, conferences, advanced research technique courses, and Master's course attendance. This does not include longer term research based training, such as Ph.D. or post-doctoral fellowships.

### 5 – TREATMENT

Research included in this category focuses on identifying and testing treatments administered locally (such as radiotherapy and surgery) and systemically (treatments like chemotherapy which are administered throughout the body) as well as non-traditional (complementary/alternative) treatments (such as supplements, herbs). Research into the prevention of recurrence and treatment of metastases are also included here.

#### 5.1 Localized Therapies - Discovery and Development

*Examples of science that would fit:*

- Discovery and development of treatments administered locally that target the organ and/or neighboring tissue directly, including but not limited to surgical interventions, cryotherapy, local/regional hyperthermia, high-intensity, focused ultrasound, radiotherapy, and brachytherapy
- Therapies with a component administered systemically but that act locally (e.g., photodynamic therapy, radioimmunotherapy and radiosensitizers)
- Development of methods of localized drug delivery
- Research into the development of localized therapies to prevent recurrence
- Guidance note: localized therapies are considered to be localized when the site of action is the same as the site of administration.

#### 5.2 Localized Therapies - Clinical Applications

*Examples of science that would fit:*

- Clinical testing and application of treatments administered locally that target the organ and/or neighboring tissue directly, including but not limited to surgical
interventions, cryotherapy, local/regional hyperthermia, radiotherapy, and brachytherapy.

- Clinical testing and application of therapies with a component administered systemically but that act locally (e.g., photodynamic therapy and radiosensitizers)
- Phase I, II, or III clinical trials of promising therapies that are administered locally
- Side effects, toxicity, and pharmacodynamics
- Clinical testing of localized therapies to prevent recurrence and prevent and treat metastases
- Guidance note: localized therapies are considered to be localized when the site of action is the same as the site of administration.

5.3 Systemic Therapies - Discovery and Development

Examples of science that would fit:

- Discovery and development of treatments administered systemically such as cytotoxic or hormonal agents, novel systemic therapies such as immunologically directed therapies (treatment vaccines, antibodies), gene therapy, angiogenesis inhibitors, apoptosis inhibitors, whole body hyperthermia, bone marrow/stem cell transplantation, differentiating agents, adjuvant and neo-adjuvant treatments
- Identifying mechanisms of action of existing cancer drugs and novel drug targets, including cancer stem cells for the purposes of treatment/identifying drug targets
- Drug discovery and development, including drug metabolism, pharmacokinetics, pharmacodynamics, combinatorial chemical synthesis, drug screening, development of high throughput assays, and testing in model systems, including that which may aid treatment planning in stratified/personalised medicine
- Investigating the molecular mechanisms of drug resistance (including the role of cancer stem cells) and pre-clinical evaluation of therapies to circumvent resistance
- Development of methods of drug delivery
- Research into the development of systemic therapies to prevent recurrence

5.4 Systemic Therapies - Clinical Applications

Examples of science that would fit:

- Clinical testing and application of treatments administered systemically such as cytotoxic or hormonal agents, novel systemic therapies such as immunologically directed therapies (treatment vaccines, antibodies), gene therapy, angiogenesis inhibitors, apoptosis inhibitors, whole body hyperthermia, bone marrow/stem cell transplantation, and differentiating agents
- Phase I, II, or III clinical trials of promising therapies administered systemically
• Side effects, toxicity, and pharmacodynamics
• Clinical testing of systemic therapies to prevent recurrence and prevent and treat metastases

5.5 Combinations of Localized and Systemic Therapies

Examples of science that would fit:

• Development and testing of combined local and systemic approaches to treatment (e.g., radiotherapy and chemotherapy, or surgery and chemotherapy)
• Clinical application of combined approaches to treatment such as systemic cytotoxic therapy and radiation therapy
• Development and clinical application of combined localized and systemic therapies to prevent recurrence and prevent and treat metastases

5.6 Complementary and Alternative Treatment Approaches

Examples of science that would fit:

• Discovery, development, and clinical application of complementary/alternative medicine (CAM) treatment approaches such as diet, herbs, supplements, natural substances, or other interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses
• Complementary/alternative or non-pharmaceutical approaches to prevent recurrence and prevent and treat metastases

5.7 Resources and Infrastructure Related to Treatment and the Prevention of Recurrence

Examples of science that would fit:

• Informatics and informatics networks; for example, clinical trials networks and databanks
• Mathematical and computer simulations
• Specimen resources (serum, tissue, etc.)
• Clinical trial groups
• Epidemiological resources pertaining to treatment
• Statistical methodology or biostatistical methods
• Drugs and reagents for distribution and drug screening infrastructures
• Centers, consortia, and/or networks
• Development and characterization of new model systems for treatment, distribution of models to scientific community or research into novel ways of applying model systems, including but not limited to computer-simulation systems, software development, in vitro/cell culture models, organ/tissue models or animal model systems. Guidance note: this should only be used where the focus of the award is creating a model. If it is only a tool or a methodology, code to the research instead.
• Reviews/meta-analyses of clinical effectiveness of therapeutics/treatments
• Education and training of investigators at all levels (including clinicians and other health professionals), such as participation in training workshops, conferences, advanced research technique courses, and Master's course attendance. This does not include longer term research based training, such as Ph.D. or post-doctoral fellowships.

6 - CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Research included in this category includes a broad range of areas: patient care and pain management; tracking cancer cases in the population; beliefs and attitudes that affect behavior regarding cancer control; ethics; education and communication approaches for patients, family/caregivers, and health care professionals; supportive and end-of-life care; and health care delivery in terms of quality and cost effectiveness.

6.1 Patient Care and Survivorship Issues

Examples of science that would fit:

• Research into patient-centered outcomes
• Quality of life
• Pain management
• Psychological impacts of cancer survivorship
• Rehabilitation, including reconstruction and replacement
• Economic sequelae, including research on employment, return to work, and vocational/educational impacts on survivors and their families/caregivers
• Reproductive issues
• Long-term issues (morbidity, health status, social and psychological pathways)
• Symptom management, including nausea, vomiting, lymphedema, neuropathies, etc.
• Prevention and management of long-term treatment-related toxicities and sequelae, including symptom management (e.g., physical activity or other interventions), prevention of mucosities, prevention of cardiotoxicities, opportunistic infections, etc.

• Psychological, educational or complementary/alternative (e.g., hypnotherapy, relaxation, transcendental meditation, imagery, spiritual healing, massage, biofeedback, herbs, spinal manipulation, yoga, acupuncture) interventions/approaches to promote behaviors that lessen treatment-related morbidity and promote psychological adjustment to the diagnosis of cancer and to treatment effects

• Burdens of cancer on family members/caregivers and interventions to assist family members/caregivers

• Educational interventions to promote self-care and symptom management

• Research into peer support, self-help, and other support groups

• Behavioral factors in treatment compliance

6.2 Surveillance

*Examples of science that would fit:*

• Epidemiology and end results reporting (e.g., SEER)

• Registries that track incidence, morbidity, co-morbidities/symptoms, long-term effects and/or mortality related to cancer

• Surveillance of established cancer risk factors in populations such as diet, body weight, physical activity, sun exposure, and tobacco use

• Analysis of variations in established cancer risk factor exposure in populations by demographic, geographic, economic, or other factors

• Trends in use of interventional strategies in populations (e.g., geographic variation)

6.3 Population-based Behavioral Factors

*Examples of science that would fit:*

• Research into populations’ attitudes and belief systems (including cultural beliefs) and their influence on behaviors related to cancer control, outcomes and treatment. For example, how populations’ beliefs can affect compliance/interaction with all aspects of the health care/service provision

6.4 Health Services, Economic and Health Policy Analyses

*Examples of science that would fit:*

- Epidemiology and end results reporting (e.g., SEER)
- Registries that track incidence, morbidity, co-morbidities/symptoms, long-term effects and/or mortality related to cancer
- Surveillance of established cancer risk factors in populations such as diet, body weight, physical activity, sun exposure, and tobacco use
- Analysis of variations in established cancer risk factor exposure in populations by demographic, geographic, economic, or other factors
- Trends in use of interventional strategies in populations (e.g., geographic variation)
• Development and testing of health service delivery methods
• Interventions to increase the quality of health care delivery
• Impact of organizational, social, and cultural factors on access to care and quality of care, including studies on variations or inequalities in access among racial, ethnic, geographical or socio-economic groups
• Studies of providers such as geographical or care-setting variations in outcomes
• Effect of reimbursement and/or insurance on cancer control, outcomes, and survivorship support
• Health services research, including health policy and practice
• Analysis of health service provision, including the interaction of primary and secondary care
• Analyses of the cost effectiveness of methods used in cancer prevention, detection, diagnosis, prognosis, treatment, and survivor care/support

6.5 Education and Communication Research

Examples of science that would fit:

• Development of generic health provider-patient communication tools and methods (e.g., telemedicine/health)
• Tailoring educational approaches or communication to different populations (e.g., social, racial, geographical, or linguistic groups)
• Research into new educational and communication methods and approaches, including special approaches and considerations for underserved and at-risk populations
• Research on new methods and strategies to disseminate cancer information/innovation to healthcare providers (e.g., web-based information, telemedicine, smartphone apps, etc.) and the effectiveness of these approaches
• Research on new communication processes and/or media and information technologies within the health care system and the effectiveness of these approaches
• Media studies focused on the nature and ways in which information on cancer and cancer research findings are communicated to the general public
• Education, information, and assessment systems for the general public, primary care professionals, or policy makers
• Research into barriers to successful health communication

6.6 End-of-Life Care

Examples of science that would fit:
• Hospice/end-of-life patient care focused on managing pain and other symptoms (e.g., respiratory distress, delirium) and the provision of psychological, social, spiritual and practical support through either conventional or complementary/alternative interventions/approaches throughout the last phase of life and into bereavement
• Quality of life and quality of death for terminally-ill patients
• Provision of psychological, social, spiritual and practical support to families/caregivers through either conventional or complementary/alternative interventions/approaches
• Research into the delivery of hospice care

6.7 Research on Ethics and Confidentiality

*Examples of science that would fit:

• Informed consent modeling/framing and development
• Quality of Institutional Review Boards (IRBs)
• Protecting patient confidentiality and privacy
• Research ethics
• Research on publication bias within the cancer research field

6.8 – Historical code [no longer used]

6.9 Resources and Infrastructure Related to Cancer Control, Survivorship, and Outcomes Research

*Examples of science that would fit:

• Informatics and informatics networks
• Clinical trial groups related to cancer control, survivorship, and outcomes research
• Epidemiological resources pertaining to cancer control, survivorship, and outcomes research
• Statistical methodology or biostatistical methods pertaining to cancer control, survivorship and outcomes research
• Surveillance infrastructures
• Centers, consortia, and/or networks pertaining to cancer control, survivorship and outcomes research
• Development and characterization of new model systems for cancer control, outcomes or survivorship, distribution of models to scientific community or research into novel ways of applying model systems, including but not limited to computer-simulation systems, software development, in vitro/cell culture models,
organ/tissue models or animal model systems. Guidance note: this should only be used where the focus of the award is creating a model. If it is only a tool or a methodology, code to the research instead.

- Psychosocial, economic, political and health services research frameworks and models
- Education and training of investigators at all levels (including clinicians and other health professionals), such as participation in training workshops, conferences, advanced research technique courses, and Master's course attendance. This does not include longer-term research-based training, such as Ph.D. or post-doctoral fellowships.
APPENDIX B: SAMPLES OF GENERAL AUDIENCE SUMMARY

1. CLINICAL AND EPIDEMIOLOGY RESEARCH

Title: Characterization of Early Breast Cancer by Contrast-Enhanced MRI

Magnetic resonance imaging (MRI) shows great promise as a supplementary tool to mammography and clinical exam for diagnosis and staging of breast cancer. Most research in this area has focused on diagnosis of invasive breast cancer. We have been interested in improving the ability of MRI to characterize early cancer, particularly at the pre-invasive stage. At the present time, the accuracy of MRI to for diagnosing pre-invasive breast disease, or ductal carcinoma in situ (DCIS) is low, mainly because the pattern of contrast enhancement for DCIS is difficult to distinguish from that of benign proliferative disease in the breast. An important emerging application for MRI is screening and surveillance in women at increased risk of developing breast cancer. There are now genetic tests and statistical models that can accurately predict a woman’s risk. However, there are few effective options for prevention and early detection. Women with a genetic risk of developing cancer are also likely to develop cancer at an early age when breast tissue is dense and mammography effectiveness is limited. MRI is very sensitive to small cancers and not limited by breast density. The studies we propose will address the specificity of MRI for early cancer and will have direct application to MRI screening and surveillance methods. We believe that in the future, a better understanding of the biological basis of patterns on MRI may lead to new methods for identifying breast tissue that is at risk for developing cancer.

2. CANCER CONTROL AND PREVENTION RESEARCH:

Title: Distrust as a Barrier to Cancer Screening and Prevention

Over the past 40 years technological advancements have had a major impact on medicine in the United States. These advancements have led to the development of effective methods in cancer screening and, most recently, cancer prevention. These methods have the potential to greatly reduce the burden of cancer, but are being threatened by the rising levels of distrust of physicians and the health care system. This project will investigate the issue of distrust with the goals of increasing understanding of health care related distrust in the US today and investigating the relationship between health care related distrust and attitudes, intentions, and behaviors regarding cancer screening and prevention.

We will focus on a population composed of African American, Caucasian, and Hispanic women to elucidate the relationship between health care related distrust and historically disadvantaged ethnic/racial minorities. These women will be between the ages of 40 and 70, a group for whom effective cancer screening is available and recommended. In order to determine the patterns of health care related distrust and association between distrust and attitudes towards cancer screening and prevention, we will conduct a population-based telephone survey in the United States. We will examine several types of cancer related health behaviors and investigate how distrust may act as a barrier to
adopting these behaviors. These behaviors will include adherence with current cancer screening recommendations for breast, cervical and colon cancer as well as willingness to use new interventions for cancer screening and prevention.

This project builds upon our prior work that has provided a more in-depth understanding of health care related distrust and established the association between health care related distrust and use of Pap smear, clinical breast examination, and influenza vaccination in the City of Philadelphia. This grant will allow us to identify the factors and beliefs the population may have about health care and physicians and determine what role distrust plays as a barrier to cancer screening and prevention. These findings will have the direct potential to improve the delivery of effective cancer screening and prevention behaviors.

3. BASIC RESEARCH:

Title: Regulation of Chromosome Segregation in Human Cells

The information which controls all of the operations of a cell is contained within its DNA, which is packaged into units called chromosomes. When a cell divides, these chromosomes must be duplicated. During duplication each chromosome is connected to its copy, therefore, the duplicated chromosomes must be properly unlinked from one another, so that each new cell receives or inherits exactly the same genetic information as all of the other cells. Errors in this process, known as chromosome segregation, results in extra chromosomes in some cells and too few chromosomes in others. Such errors are widespread among most cancer cells, and are believed to promote the growth and progression of disease. Our long term goal is to understand the molecules and mechanisms that control chromosome segregation in human cells. Towards this aim, we have begun to analyze a critical enzyme, appropriately named separase, which functions like a “molecular scissors” to split apart linked chromosomes as cells prepare to divide. Separase acts irreversibly in this process and thus needs to be controlled very precisely, to avoid potentially catastrophic errors. In this proposal, we will investigate the ways in which separase is turned on and turned off during cell division. Using a series of complementary approaches, including a novel method we invented several years ago for manipulating genes inside human cells, we will define how the chromosome-splitting process is controlled at the molecular level, and how that control ensures the high level of accuracy of chromosome segregation. Ultimately, we hope to translate this knowledge into new strategies for detecting and eliminating cells that cannot segregate their chromosomes accurately, before they have the opportunity to develop into cancers.
APPENDIX C: SAMPLE OF STRUCTURED TECHNICAL ABSTRACT

Title of Project: Structure and Function of DNA Replication Origins in Yeast

Background: The initiation of DNA replication marks a crucial step in the eukaryotic cell cycle. Entering S phase commits the cell to a full round of cell division. Studies in the budding yeast, *Saccharomyces cerevisiae*, have driven the field during the past decade, although our data and work by others suggest that many aspects of DNA replication are highly conserved in all eukaryotes, including humans. Origin structure has been best described for autonomously replicating sequence (ARS) function. Different origins have a different domain organization, and it is unclear how these differences impact the initiation of DNA replication. Recently, we have shown that initiation events occur at distinct nucleotide positions in yeast, a feature that appears to be conserved in humans.

Objective/Hypothesis: Our preliminary studies indicate that origin organization dictates where replication initiates. Therefore, we propose to define how features of ARS elements contribute to the precise initiation mechanism.

Specific Aims: (1) To determine whether chromosomal origins other than ARS1 initiate DNA replication at a distinct site; (2) to identify what determines the replication start point within origins; and (3) to determine if chromatin structure affects the initiation pattern at ARS elements.

Study design: Using a technique that we have recently developed, replication initiation point mapping, we will first map the nucleotide positions at which replication initiates in wild-type and mutant ARS elements. To address the issue of what role chromatin configuration plays in origin activation, we will analyze the nucleosomal organization of different ARS loci in relation to those regions where the parental DNA double-strand unwinds first. We will correlate the sites of initiation with sites of unwinding and place those into context with the overall chromatin structure at a given chromosomal ARS locus.

Cancer relevance: These studies will contribute to our understanding of the mechanism underlying origin activation in yeast and will aid us in understanding origin function in more complex, higher eukaryotes. Since uncontrolled origin activity directly translates into uncontrolled growth, the long-term goal of our studies is to apply our knowledge and techniques to human DNA replication in order to inhibit proliferation of cancerous cells.