

1. ACED PROJECT AWARD GUIDANCE for Understanding Disease Progression for Early Detection Call 2021/2022

ACED Project Awards fund exceptional science, to drive forward a transformational change in how and when cancer is detected through collaborative research with ACED Members.

Submit completed applications to your local ACED Programme Manager (Section 3: Useful Contacts) in Word format.

1.1. SUMMARY OF AWARD

Amount: from £200,000 to £1,000,000 (approx. \$250,000 to \$1,400,000) total award across ACED Member Centres

Eligibility: Applicants must be named Alliance Members of one of the following institutions: Canary Center at Stanford University, the University of Cambridge, the OHSU Knight Cancer Institute, University College London or The University of Manchester. Please check with your local ACED Programme Manager to ensure you are a named Alliance Member for your institution before applying.

Scope: The proposal must be within scope of **Understanding Disease Progression for Early Detection** as defined in Section 1.2 of this guidance document.

Project duration: up to 36 months

Restrictions: Each proposal must include joint lead applicants from at least two Alliance Member Centres. Collaboration between US and UK Member Centres is encouraged, but not mandatory. You must receive signatory approval from the submitting Member Centre Director for your application.

Please submit ONE application for each Project proposal; lead applicants can determine which Alliance Member Centre to submit their application through.

1.2. REMIT OF THE ACED PROJECT AWARD 2021/2022

The ACED Executive Board invite proposals for collaborative projects which explore the following question: Can the early detection of cancer be informed by an improved understanding of disease progression from early pre-malignant changes to consequential cancer?

This award provides up to three years of funding between £200,000 to £1,000,000 (approx. \$250,000 to \$1,400,000) to support pioneering early detection research, with a strong focus on innovation. Your proposed project should build on previously established research, with supporting data. If you are proposing a smaller-scale, high-risk research idea with a small amount of preliminary data, you should consider the ACED Pilot Award scheme.

The Challenge: One of the great challenges in cancer early detection research is understanding and predicting progression across the continuum of malignant transformation at every stage of the disease. Clinical cancer screening approaches are becoming more available than ever before, and the predictive accuracy of risk stratification tools continues to improve – now, more than ever, it is essential to stratify risk and predict disease progression toward lethality once an early lesion is detected. For example, breast screening identifies individuals at elevated risk of cancer (e.g. high-density breasts) and with early non-invasive lesions (e.g. DCIS). Lung screening does likewise (e.g.

ground glass opacities and indeterminate nodules). For these existing tests, there is an unmet clinical need to be able to predict which lesions are likely to progress (and so may require more aggressive strategies); this need will only grow as other screening technologies are developed. This prognostic ability will be crucial in tailoring future monitoring, early detection or interventional strategies, in order to maximise patient benefit and minimise potential harm through over-treatment or unnecessary invasive follow up.

Addressing the clinical challenge to assess the risk of cancer progression in individuals with detected early lesions from normal/at-risk to dysregulated to pre-cancerous to malignancy is essential to best tailor early detection strategies, monitoring and preventative interventions.

The Opportunity: The ACED Executive Board (AEB) have identified this challenge - **Understanding Disease Progression for Early Detection** - as a key strategic theme for the Alliance. This view was consolidated by the ACED Scientific Advisory Board (SAB) and through consultation with the wider ACED community through a recent crowd-sourcing process for open submission of “Big Ideas”.

The AEB wish to support highly collaborative research pilot projects into **Understanding Disease Progression for Early Detection**. Within the context of this challenge area, the exact nature of proposals is open to investigator-driven ideas. Example research questions (derived from the ACED community and SAB) include:

- Individuals with high germline genomic risk can exist for a long time without cancer, and then suddenly develop one - what triggered it? Are there key insults which trigger progression to cancer in those at high risk: immune dysfunction, physical trauma, infection?
- What are the factors and redundancies that *prevent* at-risk individuals from progressing? Might understanding those factors give us information that can predict low risk of progression in at-risk individuals or those with early changes?
- Can serial, longitudinal samples from cohorts of individuals provide key signals predictive of progression from healthy to early changes to invasive cancer? Can existing sample collections be harnessed to provide such insights?
- Can studying dormancy and progression to relapse provide information which gives insight into primary progression towards invasive disease?
- Can the latent stage of early lesions (when suppressor mechanisms are active) be mapped, so giving us insight into risk of progression?
- Can we understand the environmental context of the early lesion, and what changes subsequently allow it to grow/progress?
- Can the study of phenotypically normal tissue carrying what would appear to be driver mutations, compared to early and established cancers, give us insight into what drives progression?
- Are there signals in the spatial heterogeneity of phenotypically normal, premalignant and malignant tissue which predict progression?
- Can study of risk mutation carriers with and without cancer and non-carriers in the same families allow characterization of differences in germline, pre-cancerous lesion or tumour to give prognostic insight?

It is anticipated that successful proposals to this call will be highly collaborative across ACED centres and will involve team members from multiple scientific disciplines, including but not limited to examples such as:

- Methodological development
- Statistics
- Epidemiology and Risk stratification
- Genomics
- Molecular, Cell and tissue biology
- Model systems
- Biomarker discovery
- Pathology and imaging
- Technology development
- Mathematical modelling
- Clinical trials
- Oncology and medical genetics
- Cohorts and biosample collections

1.3. ELIGIBILITY

Host institution approval

To be eligible, the joint lead applicants on the Award must be named Alliance members at the following institutions: Canary Center at Stanford University, University of Cambridge, OHSU Knight Cancer Institute, University College London or The University of Manchester. Additional collaborators outside these institutions should be named in the 'Collaborative team' section of the application, clearly articulating the gaps in expertise that these collaborators provide that is not currently available within the Alliance. Collaborative Partners external to ACED must be deemed "Affiliate Members" by your Member Centre Director; these external collaborators are not eligible for ACED funding (e.g. cannot receive funds directly from CRUK but can receive funds from Alliance Member Centres if deemed reasonable and justified). **Due to specific considerations regarding data generation and sharing, you must discuss with your ACED local Programme Manager in the first instance prior to completing your application if you are planning to include Affiliate Members.**

Your Member Centre Director must approve your application before you have submitted it, so please submit your completed application to your local ACED Programme Manager (Section 3: Useful contacts) before the indicated deadline. Please contact your local ACED Programme Manager for information on required review of finances at your institution. Your proposal should also comply with all appropriate local regulatory, ethical and research governance procedures.

Applications to other funding bodies

If you are applying to other funding bodies at the same time, please note that we cannot accept the same application. If you submit an application to the Alliance that is already being considered by another funding body, your application will not be accepted.

1.4. WHAT IS FUNDED?

The Award can fund project experiments and associated running costs (including lab consumables, data storage/exchange costs, equipment, facility access charges etc.). Funds may also be used to cover postdoctoral researchers and technical staff, with associated running costs and the cost of travel and meeting organisation between collaborators named on your application. PhD students will be supported by future Alliance funding schemes and should not be included in your Project application.

If you are a UK-based lead applicant, joint lead applicant or co-investigator, you may only apply for costs to cover your own salary if you are an early- to mid-career researcher (as defined by the *Develop Independence* or *Establish Independence* career stage of [CRUK's Competency Framework](#)) and you also:

- a) meet **all** the criteria laid out in the [Policy on Salaries of Investigators](#); and
- b) can justify how the salary would support a significant career transition towards independence.

If you are an OHSU lead applicant, you must include your salary costs if you are CEDAR staff, if your home Centre is not CEDAR, you may or may not include salary costs as needed. For applications involving the Stanford Canary, a Centre full member must be included as part of the application, full list available here:

<https://canarycenter.stanford.edu/people/full-members.html>

In general, funds requested from both US and UK applicants should be directed towards direct research costs.

1.5. ASSESSMENT CRITERIA

The Alliance Executive Board will judge your proposal on:

- **Relevance to Alliance scientific strategy and remit:** All applications must be within scope of the **Understanding Disease Progression for Early Detection** 2021/2022 call as described in Section 1.2 above
- **Scientific excellence, novelty and risk:** All applications must have a strong scientific rationale to support the proposed research proposal, robust experimental design and include novel and innovative approaches. High scientific risk/high reward approaches are encouraged.
- **The challenge addressed:** What is the unmet research and/or clinical need which the proposal would address within the scope of the **Understanding Disease Progression for Early Detection** call? How would knowledge be advanced to meet that need?
- **Line of sight to clinical/population impact:** The proposed work must have the potential for a remarkable impact on cancer detection. Whilst not all applications will be translational in nature, it is important that all research is designed with a clear line of sight to clinical/population impact and the proposal should clearly articulate this pathway and the evidence and outputs that will be required to advance along it. Appropriate consultation/collaboration with clinicians, population scientists, industrial partners, patients and/or the public should be included to facilitate this.
- **Excellent team and collaborative environment:** All applications should outline the suitability and feasibility of the lead applicants (and supporting roles) to carry out the proposed research with access to the resources and facilities required for the successful fulfilment of the award.

Applications should highlight the importance of the Alliance environment in supporting the potential of the proposed research and address how Alliance partnerships will uniquely enable the proposed research compared to Alliance Member Centres conducting the research independently. Multidisciplinary, transatlantic collaboration is encouraged when appropriate to the science proposed. It is important to demonstrate the added value of the proposed collaboration and the individual contributions, as well as the steps taken to ensure an effective collaboration.

- **Resources requested:** The costs requested in an application should, in general, be for the direct costs of the research and reasonably justified in line with the experimental plans, leveraging existing resources where appropriate.
- **Benefit to the wider Alliance:** Applications should detail the actual and potential benefits to the wider Alliance community, including any infrastructural benefits, knowledge exchange, data sharing, etc.

2. THE APPLICATION PROCESS

2.1 PROCESS OVERVIEW

Complete the provided template and submit your application to [your local ACED Programme Manager](#) before the indicated deadline. Following submission, applications are sent for expert peer review within the Alliance membership when possible, to help provide constructive feedback to strengthen your proposal. Applicants will have the opportunity to respond to peer reviewers' comments. Following this, applications are considered at a meeting of the Alliance Executive Board, where funding decisions are made.

2.2 RESEARCH PROPOSAL

Please use the template provided to complete your research proposal (Section 4.2 of the Project application template). **Section 4.2 of the application template should not exceed eight standard pages using Arial 10-point font, including figures. References are not included as part of the page restriction. In this section, you should aim to address the content outlined in the table below.**

In your research proposal please include:

- How the proposal will help establish your research in the early detection field in the scope of the **Understanding Disease Progression for Early Detection 2021/2022** call
- The novelty of your idea
- The strength of your collaborative team to achieve the endpoints of your proposal
- The downstream translational potential of your idea
- The clinical need addressed by your idea
- The contribution to early detection research should the idea be a success
- Outline any examples of similar and/or competing approaches globally, for the proposed research (e.g. different test to determine the same outcome, different cohorts, etc.).
- If there are commercial collaborators, outline the intellectual engagement and financial investment contributed by the commercial entities, and how this is critical to the proposed research.

Contents of the research proposal

<p>CHALLENGE</p>	<ul style="list-style-type: none"> Clearly describe the hypothesis for your proposed project. Briefly describe the scientific need for your proposed work – why is it necessary to test this hypothesis? If your proposal is for discovery research, this is an opportunity to provide context around the clinical need and how your results could lead to impact for patients. Describe the significance of the results you plan to obtain. In particular, the relevance of your expected results to detection of cancer – for example, any future clinical applications or impact on policy and practice.
<p>BACKGROUND</p>	<ul style="list-style-type: none"> Summarise your current and other published work relating to your research proposal, including the major achievements of your collaborative team over the last 5 years. You might refer to any relevant preprints or datasets in a citable format (e.g. including a unique Digital Object Identifier). Describe how this knowledge and experience can be integrated to address the goals and hypothesis of the proposed research project.
<p>RESEARCH PLAN</p>	<p>This section is highly important and therefore we suggest you devote a substantial proportion of your research proposal to it.</p> <p>We suggest you divide your research plan into objectives. For each objective state:</p> <ul style="list-style-type: none"> Experimental methods, techniques and analyses that you'll use to test your hypothesis. Refer to your own published work where you've used these methods before or indicate the availability of appropriate expertise. Justify the appropriateness of your experimental design including sample size calculations as appropriate Any available unpublished research findings or methodologies supporting your research proposal (please include these in the text, not as an appendix). Explain clearly how you will address the early detection challenge you have identified. Please provide enough information on how you plan to develop your ideas and build a platform for future research, highlighting the key milestones necessary to achieve this. Briefly describe what the major achievements of your research will be, if the project is successful. Clearly articulate how these outputs could be taken forward along the translational pathway towards earlier detection of cancer in patients. You also have an opportunity in this section to describe how you plan to involve patients and the public in your research, if relevant.
<p>TEAM COMPOSITION</p>	<p>Please provide information on the composition of the team of applicants and collaborators including:</p> <ul style="list-style-type: none"> Whether the team or members of the team have published together previously (this is not a requirement). Individual time contributions of those working on the project where possible, stating briefly the added value of the collaboration compared to each researcher working independently. Address how the Alliance environment is critical in supporting the potential of the proposed research and how this Alliance partnership will enable the proposed research compared to Alliance Member Centres conducting the research independently.

TIMESCALE AND POTENTIAL PROBLEMS	<ul style="list-style-type: none"> • Provide a table to indicate milestones and time-scales for each part of the plan. • List potential logistic or scientific problems and suggest solutions or alternative plans.
REFERENCES	<ul style="list-style-type: none"> • Give full details of any references, including authors, publication year, title and journal name, volume, page numbers. We won't accept shortened references. • Number your references in the order in which they appear in the text, and list them in the Vancouver style (as outlined by the US National Library of Medicine).

2.3 ADDITIONAL RESEARCH INFORMATION

Please use the provided template to complete the following sections.

Additional information for all proposals

JUSTIFICATION FOR SUPPORT REQUESTED	<p>Please complete these sections according to the following guidelines. Costs should be divided and reported separately for each UK and US Member Centre(s) in the local currency of the country in which they are incurred in (e.g. GBP (£) for UK and USD (\$) for US). For example, if a cost is associated with research conducted at US Member Centres, it should be reported as <i>Stanford or OHSU- USD (\$) amount</i>. Costs associated with research at UK Member Centres, should be reported as <i>Manchester or Cambridge or UCL - GBP (£) amount</i>.</p> <p>Please list all costs (staff, running expenses and animal costs) and provide scientific justification for the associated costs in the relevant box on the application form. Please insert extra rows in the table to enable you to detail all of the costs.</p> <p>For translational ACED Project Award applications that require access to clinical infrastructure, applicants should investigate other sources of funding for staff employed to work across multiple research projects rather than solely on the ACED Project Award (e.g. data managers and research nurses). Where possible existing infrastructure from the research centre to which the applicant belongs to should be used.</p> <p>Staff: For awards requesting multiple staff, it should be clear from the justification how staff will be deployed across the different components of the research project over the course of the grant. Postdoctoral researchers can be included in your request.</p> <p>PhD Students: Funding for ACED PhD Students will be supported through a separate funding scheme (to be launched in future); requests should not be included in your Project application.</p> <p>Patient Involvement: List the overall costs for the patient/public involvement activity planned in your proposal, including travel, accommodation and subsistence costs, and honoraria. Reasonable costs for these activities are detailed in our Costs Guidance.</p> <p>Running Expenses: Please list lab consumable costs for each staff member.</p>
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	<p>Please list specific costs separately from general consumables. Please list any requested equipment under £5000/\$6500.</p> <p>Equipment: Please tell us about all the equipment you'll require for the full duration of your award. If there is equipment you'll only need in the later years (2-3), please note this in your application; include any equipment that costs < £5,000/\$6500 as a running expense. Please provide details and scientific justification for any items of equipment (over £5000/\$6500) requested in this section. Include any details of contribution(s) made to the purchase of equipment by the host institute.</p> <p>Example table:</p> <p>6.2 Running Expenses</p> <table border="1"> <thead> <tr> <th>Description</th> <th>Additional Information</th> <th>Costs Year 1</th> <th>Costs Year 2</th> <th>Costs Year 3</th> <th>Costs Total</th> </tr> </thead> <tbody> <tr> <td>Data storage (Cambridge)</td> <td>Storing data from RNAseq and DNaseq data and respective public datasets for subsequent analysis</td> <td>£0</td> <td>£3200</td> <td>£0</td> <td>Cambridge - £3200</td> </tr> </tbody> </table>	Description	Additional Information	Costs Year 1	Costs Year 2	Costs Year 3	Costs Total	Data storage (Cambridge)	Storing data from RNAseq and DNaseq data and respective public datasets for subsequent analysis	£0	£3200	£0	Cambridge - £3200
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<p>STATISTICAL DESIGN AND ANALYSIS PLAN</p>	<p>For each research question as appropriate:</p> <ul style="list-style-type: none"> • Describe the statistical analysis used; • Name the variables and describe the values; • State the numbers of samples you plan to include in each analysis, describing what you can achieve with this number of samples; • Include (where appropriate) the associated level of statistical power; • Suggest any potential limitations; • Clarify other relevant details (e.g. numbers of events in clinical outcomes, length of follow-up for clinical outcomes). 												
<p>CELL LINES</p>	<p>Only complete if applicable</p> <p>Please provide details of any cell lines you will use in your research. These should include:</p> <ul style="list-style-type: none"> • Details of how you will maintain good cell culture practices throughout your research project. • If new cell lines will be introduced to your lab, please give the source will be authenticated when they enter your lab. • If new cell lines will be generated, please tell us how these will be made available for others to use. • Justification for the use of any cell lines that have been misidentified (e.g. Chang liver cells). <p>You can request funding (under running expenses) to support cell line authentication (e.g. screening for contamination by mycoplasma, STR profiling for human cell lines or DNA fingerprinting for non-human cells). You'll need to validate your cell lines according to the Guidelines for the use of cell lines in biomedical research</p>												

(doi:10.1038/bjc.2014.166), which should be referenced in any publications resulting from the award.

ANIMAL STUDIES

Only complete if applicable

You should complete this section if you are proposing to use animals in your research. You should ensure you are familiar with the relevant [NC3Rs guidelines](#), in particular the [Responsibility in the Use of Animals in Bioscience Research](#) document, the [ARRIVE Guidelines](#), and the [NC3Rs Guidelines: Primate Accommodation, Care and Use](#). When completing this section, you should describe how your proposed research adheres to the expectations set out in these guidelines.

Animal Costs:

- Please include a full breakdown of the purchase costs and husbandry costs (e.g. per mouse per week).
- Please list animal purchase, maintenance and experimental costs separately.

Justification of proposed animal studies

Please briefly justify the use of animals by outlining:

- Why animal research is necessary for your award and details of all species you propose to use;
- Why the species/model you have chosen is the most appropriate physiological model to use for the research objective(s);
- If you are developing any new models why this is necessary and how you will ensure that these will be disseminated to the research community more broadly;
- The efforts you will take to minimise animal usage.

For your critical experiments, please provide an outline of your experimental design and power calculations. Where details of specific experiments are not known, you may provide an illustrative example. This should include:

- An overview of the experimental approach summarising; primary and secondary experimental outcomes, number of experimental and control groups, the number of experimental units in each experimental group, the total number of experimental units to be measured and the number of times each unit will be measured, number of independent replications of each experiment and how you plan to minimise experimental bias (e.g. randomisation and blinding) or an explanation of why this would not be appropriate.
- An explanation of how effect sizes have been calculated and a justification of their biological relevance
- The power calculations used to determine your sample size (or a principled explanation of an alternative basis for calculations, justifying why you haven't used statistical calculations). Explanations based solely in terms of 'usual practice' or previously published data will not be considered adequate.
- Details of breeding strategies that will be implemented (if applicable).
- A brief description of your planned statistical analyses in relation to the sample size, and list any statistical advice available.
- You may present this in the form of a table or diagram, if appropriate.

Please note that the NC3Rs website includes a number of useful [experimental design resources](#), including the Experimental Design Assistant (EDA), a free online tool to help optimise experimental design. The EDA can be used to create a visual map of your planned experiments (or a few of them) that may be useful in discussions with your team and statistical advisors. If you use the EDA, you are encouraged to submit the EDA report as a PDF upload.

Please note that applications proposing research on specially protected species (cats, dogs, equines or non-human primates) or pigs must undergo an additional independent peer review by the NC3Rs; contact the office as soon as possible (and before the application deadline date) if this is applicable to your proposal.

For any animal studies to be performed outside of the UK, we also require a letter to be included with your completed application from the relevant applicant leading this work to confirm that the research proposed will adhere to all relevant local regulatory systems, and also that the welfare standards will be consistent with UK standards.

2.4 ADDITIONAL DOCUMENTS

Letter(s) of Support: If you are listing collaborators external to the Alliance, you must include a brief letter of support as evidence of their commitment to your proposal. Submit any Letters of Support in PDF format, signed, dated and on headed paper alongside your completed application.

2.5 ETHICAL APPROVAL

If you plan to involve patient tissue or patient information in your research, you'll need to get ethical approval. You do not need ethical approval for Patient Involvement activities however we do expect best practice to be followed (resource: NIHR National Standards on Patient Involvement in Research). It's **your** and **your Host Institution's responsibility** to make sure you comply with all legal requirements and ethics approval. We understand that you'll generally need to confirm funding arrangements before you can get ethical approval. Therefore, we can make you a provisional offer of funding, but we may not release any money to you until you've sent us written confirmation of ethical approval. Please bear this in mind when you propose a start date for your award. If you need any other regulatory approval, we may also need written confirmation before we release funding. We will review this on a case by case basis.

2.6 PATIENT AND PUBLIC INVOLVEMENT

While we do not mandate inclusion of specific involvement activities as part of your research, if your proposal involves studies utilising patients and the public, their samples or data, we would highly encourage you to include patient and public involvement plans if they can add value to your research proposal.

This could include, but is not limited to, involvement in the development of research questions, planning/design of research, patient recruitment, monitoring progress, evaluation and/or dissemination of research findings. This could also include offering advice as members of a project steering group, commenting on or developing research materials.

You may like to address the following prompt questions when writing about your PPI plans in your application. You are not required to follow this format.

- What is the proposed PPI plan? What is the rationale for the plan?
- How many people are you aiming to involve through the activities set out in your plan? What is their role? How will you recruit them?

- How will you support those who you involve in your research?
- What is the proposed budget required for your PPI plan?

Resources to help you:

CRUK provides details and guidance on how to implement patient and public involvement (PPI) plans, including budgeting and cost guidance in the [PPI toolkit for researchers on our website](#). To request login details to access the toolkit, or for any additional questions regarding patient involvement, please email involvement@cancer.org.uk.

[INVOLVE](#): provides briefing notes on how to involve patients at each stage of the research cycle

[NIHR Research Design Service](#): can offer application specific support and advice on appropriate public and patient involvement methods.

[People in Research](#): can be used to advertise involvement opportunities and recruit people.

[NCRI Consumer Liaison Forum](#): Many forum members also act as patient representatives in their local area or for other national bodies such as the Department of Health or Public Health England.

3. USEFUL CONTACTS

Once you have read these guidelines, please contact ACED@cancer.org.uk if you have any questions. Your local programme manager can also provide information related to questions for your specific location.

Affiliation	Name	Role	Contact Information
Cancer Research UK	Karolin Kroese	ACED Programme Manager	Karolin.Kroese@cancer.org.uk
Cambridge	Wendy Alderton	Programme Manager	wa266@cam.ac.uk
University College London	Daniel Kelberman	Programme Manager	d.kelberman@ucl.ac.uk
OHSU	Erin Watson	Programme Manager	watsoner@ohsu.edu
Stanford	Ryan Spitler	Programme Manager	rspitler@stanford.edu
Manchester	Martin Bone	Programme Manager	martin.bone@manchester.ac.uk