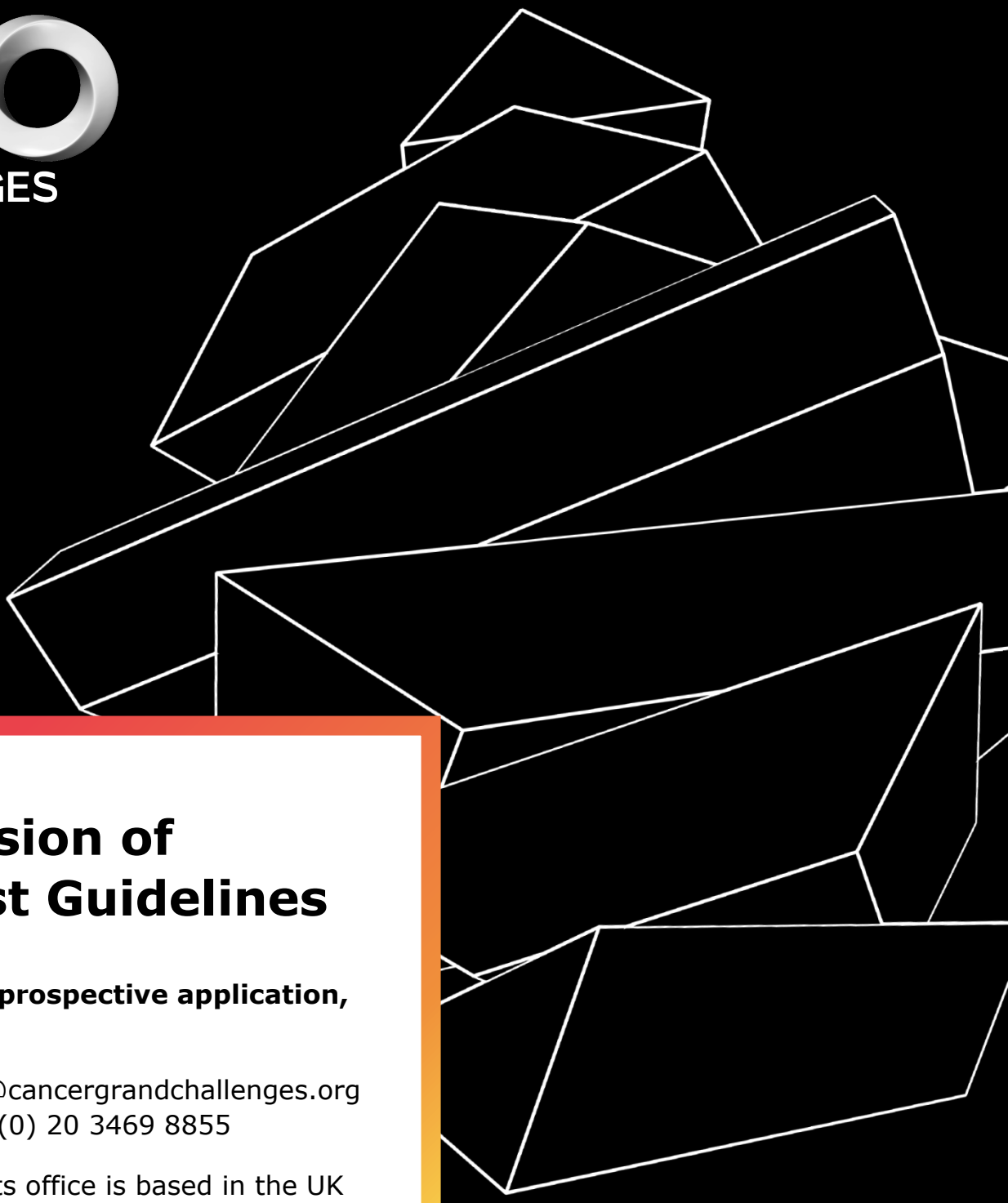
CANCER GRAND CHALLENGES



Expression of Interest Guidelines

To discuss a prospective application, please:

email info@cancergrandchallenges.org
phone +44 (0) 20 3469 8855

Note our grants office is based in the UK so responses may be slower outside of British working hours.

Founded by

CANCER RESEARCH UK

NIH NATIONAL CANCER INSTITUTE

Expression of Interest Guidelines

Table of Contents

1. SUMMARY OF KEY DATES

1. Complete questionnaire	2. Submit EOI	3. Shortlist	4. Submit full application	5. Award starts
01 April 2021	22 April 2021	May 2021	October 2021	2022

1. COMPLETE PRE-SUBMISSION QUESTIONNAIRE

Decide which of the Cancer Grand Challenges your team will tackle, and submit a pre-submission questionnaire on our website. This will be used to check eligibility against the criteria set out in Sections 3 and 4 of these guidelines.

2. EXPRESS YOUR INTEREST

Once you have had an application opened by the Cancer Grand Challenges office team, submit an Expression of Interest (EOI) outlining your team and the approach you'll take to address the challenge.

3. COMMITTEE SHORTLISTS TEAMS

The Cancer Grand Challenges Scientific Committee (CGCSC) will recommend which EOIs should be shortlisted.

The chair of the Cancer Grand Challenges Advocacy Panel (CGCAP) will participate in the Scientific Committee meeting. The panel will then review the patient advocate involvement and engagement plans in shortlisted EOIs.

Each shortlisted team will be awarded up to £30,000 seed-funding to get their teams off the ground and to help formulate their full application.

4. FULL APPLICATION AND INTERVIEW

Shortlisted teams submit a full application and attend an interview with the CGCSC.

The CGCAP will review the patient advocate involvement and engagement plans in the full written applications and provide feedback to both successful and unsuccessful teams.

5. AWARD

Winning team members collectively enter into a Cancer Grand Challenges Award Agreement with one another, and with Cancer Research UK and the National Cancer Institute (NCI). Each team member will be issued with their proportion of the award through a Grant Award Letter from Cancer Research UK and a Notice of Award from NCI.

2. VISION FOR CANCER GRAND CHALLENGES

Cancer Grand Challenges is a global funding platform founded in 2020 by the two largest funders of cancer research in the world: Cancer Research UK and the National Cancer Institute in the US. This partnership builds on the success of Cancer Research UK's Grand Challenge, launched in 2015 and supporting currently supporting seven multidisciplinary teams across nine countries.

By daring global teams of multidisciplinary researchers to come together and think differently, we can find bold new solutions to challenges which have confounded scientists for many years.

We set ambitious challenges to inspire new thinking, providing diverse, global teams with £20m ($25m) over five years to unleash their scientific creativity.

Each step in the Cancer Grand Challenges process – identifying the challenges, reviewing the scientific proposals, supporting the best multidisciplinary teams – has been designed to foster high impact cutting-edge research and scientific creativity.

The ideas for potential Cancer Grand Challenges are identified through extensive discussion with the cancer research community and people affected by cancer. These challenges are intended to be major research hurdles that can only be addressed through large scale efforts typically involving multiple institutions and multidisciplinary teams. By setting these challenges, we aim to foster global alliances that have the potential to transform how we prevent, diagnose and treat cancer.

Collaboration, innovation and creativity are at the heart of Cancer Grand Challenges, we believe the greatest progress can only be made when scientists share knowledge, expertise and experience. Through Cancer Grand Challenges we aim to create a global community that will accelerate progress in the fight against cancer.

3. WHAT DO WE WANT TO SEE FROM APPLICANTS?

Cancer Grand Challenges are intended to transform cancer research. Therefore, we are looking for applications that reflect this ambition. We want to see proposals for bold, innovative solutions to the challenges we have set, and to see evidence that applicants have actively sought out new, perhaps unusual, collaborations that will bring fresh thinking to these currently intractable problems. Cancer Grand Challenges are not intended to fund research that would be fundable by other response-mode schemes and initiatives.

Cancer Grand Challenges are not single investigator-led awards – they should involve investigators from institutions across the globe, and from different disciplines. Ultimately, we are looking for the best teams with the best ideas to address the challenges. We also anticipate that proposals will drive global collaboration and bring together diverse expertise in a way that is not already happening. Including non-traditional disciplines is encouraged, both to drive the development of novel technologies or methodologies and to incorporate thinking from other fields that has not yet been applied to cancer. Underpinning this, involving people affected by cancer is also required to ensure the research is focused on the needs of patients.

The end point of a Cancer Grand Challenges award does not need to be a clinical intervention or clinical impact within the duration of an award. To the greatest extent possible and appropriate, research plans to address a challenge should have a clear line of sight towards preventing, diagnosing or treating cancer.

3.1. ASSESSMENT CRITERIA

The CGCSC will review EOIs based on:

- **Relevance**: there must be a clear plan to address the challenge as it has been articulated.
- **Quality**: the work proposed must be of the highest international scientific calibre.
- **Innovation**: the work must involve the development of new methodologies, tackling the challenge in a novel way rather than scaling up existing experimental approaches.
- **Team**: the very best team should be assembled to address the challenge. The team must
  - Be multidisciplinary, attracting new thinking to cancer research;
  - Be international, facilitating global collaboration between researchers;
  - Incorporate training for future leaders in cancer research.
- **Impact**: the ambition must be that the results of the work proposed will be transformative in how cancer patients are diagnosed or treated, or how people are prevented from developing cancer.

4. CHALLENGE TEAMS

We expect applicants to outline the most appropriate make-up of their team and to carefully consider the way the team will be structured and managed.

At EOI stage, we expect a team to include a Principal Investigator (PIs) and multiple Co-Investigators (Co-Is). There should also be a plan for how the team will recruit one or more appropriate patient advocates. Funded teams will also be required to recruit a full-time programme manager to coordinate the research consortium, make sure that milestones are being met, facilitate team communication and interface with the funders.

Teams are not necessarily expected to have recruited patient advocate(s) or identified a potential programme manager at EOI stage.

We also expect that teams will be international in nature, with no more than 70% of the activity (and funding) being based in a single country. There is no requirement for teams to be led by, or comprise team members, who are based in the UK or US.

Applications to address one of the challenges are welcomed from teams working across a breadth of disciplines and institutions including but not limited to: the biomedical sciences, software development and technology, engineering and physical sciences, behavioural, health, population and social sciences.

The chances of Cancer Grand Challenges teams reaching their objectives are greatly increased by ensuring they draw on members of diverse backgrounds and experiences. As such, we strongly encourage applicants to consider team diversity at the earliest possible opportunity. We are particularly interested to see teams with Co-Is who are in the early stage of establishing their independent careers.

CGCSC members are excluded from applying; other researchers from their host institutions can apply.

4.1. PRINCIPAL INVESTIGATOR

Each team must have a Principal Investigator, who will be the person responsible for the overall scientific and technical direction of the team, as well as being the lead administrative contact. The PI must ensure that team members comply with the Terms and Conditions of the award, and will be the primary contact for the Cancer Grand Challenges office team.

The PI must be based at a research institution which is appropriately accredited or registered in the country in which it is based. Applications cannot be led from commercial entities.

PIs cannot be named as PI on more than one Cancer Grand Challenges EOI, but may be named as a Co-I on more than one EOI.

4.2. CO-INVESTIGATORS

Teams should include multiple Co-Investigators, who will provide significant intellectual input into the Cancer Grand Challenge, and lead/contribute to individual work packages.

Each Co-I will be responsible for the scientific and technical direction of their work package and, as such, will be responsible for contractual and financial obligations, and other organisational assurance/certifications that fall within that work package.

Academic/commercial collaborations are encouraged where appropriate. Co-Is may therefore be based at commercial entities, but requests for funding to these will be considered only for small and medium-sized enterprises (SMEs), and on a case-by-case basis. Both commercial entities and research institutions named on Cancer Grand Challenges applications must be appropriately accredited or registered in the country in which they are based.

Note whilst we have not set a limit on the number of Co-Is per team, it should be clear in the EOI that any individual named as a Co-I will make a significant intellectual contribution to the team – and we would expect all Co-Is to receive significant funding in order for them to make a substantial contribution to a team. Teams funded in previous rounds of the initiative have involved between five and 13 Co-Is.

4.3. COLLABORATORS

Additional academic or commercial collaborators can be included within work packages. You do not need to include these in the EOI, but they will be requested at the full application stage.

4.4. PATIENT ADVOCATES

Applicants must look for opportunities to involve advocates for people affected by cancer (patients, survivors, caregivers) in their research. We believe that involving people affected by cancer through meaningful and impactful patient advocate involvement and engagement activities ensures patients' needs are always at the heart of research and that there are clear and significant benefits for patients.

If shortlisted, teams will be expected to recruit a minimum of one patient advocate with a clearly defined role and remit. Patient advocates bring the perspectives of those affected by cancer to the work of a Cancer Grand Challenges team. They represent people affected by cancer as a group and should not provide just their individual viewpoint or that of any advocacy organisation. The patient advocate(s) will work with the PI and Co-Is as a member of the team to develop the involvement and engagement strategy into a detailed plan that will be refined over the first year of the award if funded. They will then be critical in delivering and implementing the plan over the lifetime of the award.

If funded, we expect you to meaningfully consult, collaborate and partner with your patient advocate(s) at all stages of the research programme where such interaction can add clear value and accelerate progress.

Please refer to our additional information about patient advocate and involvement for more information about the role of patient advocates and about building your advocacy strategy from EOI stage onwards.

4.5. PROGRAMME MANAGER

Funded teams will be required to recruit a full-time programme manager to coordinate the research consortium, with responsibilities which could include, but aren't limited to:

- Making sure that milestones are being met;
- Facilitating team communication, as well as communicating frequently and directly with leadership across participating institutions;
- Interfacing frequently with the funders;
- Ensuring timely publication of findings, availability of high-quality data and proper IP management;
- Preparation for annual reviews and site visits.

Programme managers should have experience managing large multidisciplinary and multi-institutional efforts, or the capacity to do so. We advise that applicants begin to consider their specific requirements for a programme manager as early as possible. Although there is no expectation that an individual who could fill the role will have been identified at EOI or full application stage, full applications will need to include a governance and delivery plan which will include the expected requirements and role responsibilities of the programme manager.

5. AWARD TERMS AND CONDITIONS

To receive Cancer Grand Challenges funding from Cancer Research UK and NCI, teams will be required to agree to a set of funding policies. An Award Management and Funding Policy Guide will be made available to shortlisted teams. The guide will detail the terms and conditions of the award, and set requirements for use of the funding and for the governance of the award. The CGCAA will also set out the arrangements for reporting, the ownership and use of intellectual property rights, confidentiality, publication of results, exchanges of information and materials, and related issues.

Members of Cancer Research UK and NCI staff will meet with shortlisted teams to address any questions they may have about the guide.

In agreeing to the funding policies, all funded institutions will enter into a Cancer Grand Challenges Award Agreement (CGCAA) with Cancer Research UK and NCI.

By submitting an EOI, each applicant team agrees that, if shortlisted for the award, the Cancer Grand Challenges office team may include the names, affiliations and photographs of the team members, together with a summary of the shortlisted research proposal in materials we may produce to publicise and promote Cancer Grand Challenges.

5.1. USE OF YOUR DATA

For the purposes of administering the EOI process for Cancer Grand Challenges, Cancer Research UK will act as the operational manager and be responsible for the collection and proper handling of all data provided by applicant teams.

Because Cancer Grand Challenges will be funded jointly with NCI, based in the United States, it is necessary for Cancer Research UK and NCI to share personal data from any application. The data that will be shared will be: researcher names; job titles/positions; host institutions/organisations and locations; professional qualifications, positions and accolades; current research programmes; contact details (email and phone); and salaries.

Stricter controls and protections apply to the processing of personal data under UK and European law (including the General Data Protection Regulations) than generally apply to the processing of data in the United States. For example, though States may have their own Data Protection laws and authorities, there is no federal equivalent to the Information Commissioner's Office which receives complaints concerning the processing of personal data in the UK.

In submitting an EOI, the PI will be required to confirm on behalf of each named researcher (or collaborator) on the application, that you consent to the personal details listed above being shared by Cancer Research UK with NCI.

You may withdraw consent for your data to be shared with NCI by withdrawing your application for Cancer Grand Challenges funding. To do so, email info@cancergrandchallenges.org.

6. WHAT WE WILL FUND

Each team is required to provide an approximate breakdown of the proposed phasing of these costs against each work package in their EOI.

Cancer Grand Challenges awards provide up to £20 million for the direct costs of research (research staff, associated running costs and equipment) and all patient advocate involvement and engagement activities. Direct costs are those costs that arise from the conduct of the research undertaken and are verifiable from accounting records.

Each institution hosting a component of a Cancer Grand Challenges award will be individually issued their proportion of the direct costs. ~50% of the direct costs will be issued in pounds sterling (GBP) by Cancer Research UK in the form of a Grant Award Letter; ~50% will be issued in US dollars (USD) by NCI in the form of a Notice of Award.

In addition to the direct costs of research, some institutions may be eligible to charge for indirect costs. Indirect costs may include costs charged on estimates or apportioned costs; management and administrative costs; and costs related to buildings and premises.

For all funding issued to institutions based in the UK:

- Cancer Research UK will not fund indirect costs;
- NCI will consider funding indirect costs up to 8% of the value of the direct costs of research funded at that institution.

For all funding issued to institutions based in the US:

- Cancer Research UK will consider funding indirect costs up to 10% of the value of the direct costs of research funded at that institution;
- NCI will generally reimburse indirect costs using the institution's federal negotiated indirect cost rate. Any institution that has never received a negotiated rate may propose a rate with a justification and National Institutes of Health (NIH) will determine the rate for the awards.

NCI will not fund indirect costs in any jurisdictions other than the US or UK.

Cancer Research UK will consider funding indirect costs to institutions only in jurisdictions where indirect costs are typically funded through charitable or public research grant funding, up to 10% of the value of the direct costs of research funded at that institution. Most European countries do not use this funding model and so indirect costs would not be paid.

Direct costs of team members based at commercial (rather than academic) institutions may be supported, but will be considered only for small and medium-sized enterprises (SMEs), and on a case-by-case basis.

7. HOW TO APPLY

To apply for a Cancer Grand Challenges award, please complete the following steps:

7.1. CREATE A CANCER RESEARCH UK FLEXI-GRANT ACCOUNT

EOIs will be submitted through Cancer Research UK's grants management system, Flexi-Grant. If you have previously logged into Cancer Research UK's old system, eGMS, you already have an account.

Visit cancerresearchuk.flexigrant.com.

If you have previously logged into eGMS:

- Click 'login'.
- Enter your registered email address.
- You will need to reset your password. Click the 'Forgot password?' link and follow the onscreen instructions.

If you have not previously logged into eGMS, click 'Register' and follow the onscreen instructions.

Once you have logged into Flexi-Grant, please note that you will not find the option to begin an EOI for Cancer Grand Challenges on the 'Start application' page. A form will be opened for you once you have completed the following step.

7.2. PRE-SUBMISSION QUESTIONNAIRE

Before we can give you access to an EOI form on Flexi-Grant, the PI must submit a short questionnaire to the office. This information will be used to check eligibility against the criteria set out in Sections 3 and 4 of these guidelines.

This information will not be disclosed to the CGCSC and is not part of the formal scientific review process. We do not require a full list of Co-I names at this stage; where you are yet to confirm a position, please provide an indication of discipline.

It typically takes up to one week to process your questionnaire, so the deadline for submission is 01 April 2021, three weeks in advance of the EOI deadline.

7.3. EXPRESSION OF INTEREST

The Cancer Grand Challenges office team will let you know when your EOI application form is set up on Flexi-Grant. The deadline for EOIs is 22 April 2021. Please note that due to the large volume of EOIs anticipated, the CGCSC may not be able to provide feedback to unsuccessful applicants.

You will be required to provide the following:

- Public-facing publishable research abstract (this may be used on our website, to help Cancer Research UK in fundraising activities, and for other general purposes so should not include any confidential information).
- Upload comprising:
  - Completed EOI template (Section 7.4);
  - Completed Biosketch template for the PI and all Co-Is (Section 7.5).

The vision and broad ambition for your proposal should be accessible to all scientific disciplines. However, please ensure that you include relevant and sufficient detail and depth related to the scientific approach that underpins the vision. Note, this does not have to be tailored to a broad audience and should discuss specific technologies and methodologies that will be employed.

7.4. EXPRESSION OF INTEREST TEMPLATE

The EOI template will give you space to provide an overview of your team's approach to solving your selected challenge. This template will be provided in Flexi-Grant, but the table below outlines the sections that you will be asked to complete in your proposal.

Section of EOI template	What it should cover	Word count
Team	Brief description of your Cancer Grand Challenges team	n/a
Summary	Overview of your team's approach to solving the challenge	
	• Description of the proposed research	1,500 words
	• Rationale for team make-up	500 words
Outputs and impact	Expected outputs and impact of your proposal	1000 words
Patient advocate involvement and engagement	Strategy for involvement of people affected by cancer in your scientific programme; and how you will engage the public with your research. Please refer to our additional information about patient advocate and involvement.	500 words
Financial overview	Predicted spend for each work package, over the five years in pounds sterling (GBP) Any capital requests in excess of 5% of the likely total Cancer Grand Challenges award spend	n/a

7.5. BIOSKETCH UPLOAD

Each team is required to upload a completed Biosketch form for the PI and all Co-Is. Each Biosketch should not exceed two sides of A4.

Section	Detail
Academic details	Name, Position, Institution, Location Professional qualifications Positions and accolades
General	What are your five greatest contributions to research? Current research programmes

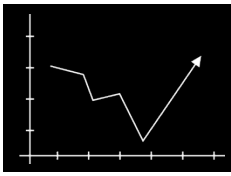
7.6. CANCER GRAND CHALLENGES HELPLINE

For more information or to talk about opening an application, please contact our dedicated Cancer Grand Challenges Helpline. Note our grants office is based in the UK so responses may be slower outside of British working hours.

email info@cancergrandchallenges.org

phone +44 (0) 20 3469 8855

8. THE CHALLENGES



Understand and reverse cachexia and declining performance status in cancer patients

CONTEXT

Many patients with advanced cancer suffer from a devastating syndrome termed cachexia. This is characterised by significant weight loss from both loss of skeletal muscle and fatty tissue that can't be reversed by nutritional support. These symptoms are often accompanied by fatigue and a declining performance status that imparts a poor prognosis. Understanding the causal mechanism of this syndrome would open the door for the development of novel interventions, which could improve treatment response, quality of life, and survival.

BARRIERS AND OPPORTUNITIES

Cachexia, fatigue, and poor performance status are common problems in patients with advanced cancer. Although there is a limited understanding of the molecular basis of these clinical phenomena, current research has suggested that these may be a result of a complex set of interactions between the tumour and the patient that includes release of inflammatory cytokines and tumour and host metabolic changes. Research has begun to uncover some cancer cell intrinsic mechanisms, but we know little about how tumours interact with the stroma and host in this setting. Pre-clinical and clinical studies have generated plausible mediators of cachexia, however, there has been little impact on patient benefit when such mediators are targeted in clinic.

This calls for bold new approaches to better understand and treat cachexia, fatigue and declining performance status. This might include:

- Generating a deeper molecular understanding of cachexia and fatigue
- Can preclinical models be developed that recapitulate these conditions?
- Can we identify methods to manipulate the pathways involved and identify treatment targets?
- Are there biomarkers predicting the onset of cancer cachexia? And once identified could these lead to the development of biomarker driven clinical trials to prevent or reverse its onset?

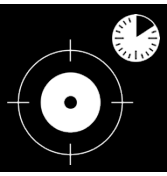
VISION AND IMPACT

This challenge seeks to expand our mechanistic understanding of cachexia, fatigue, and poor performance status that severely impact the quality of life of cancer patients and limit our ability to deliver systemic therapies. Please note, although we recognise that many patients may have prolonged

treatment-related fatigue, the focus of this challenge should be on addressing and reversing the causal mechanisms of cancer cachexia, declining performance status and fatigue independent of therapy.

It will require a multidisciplinary research team that could include expertise in metabolism, endocrinology, biology, immunology, neurohormonal biology, clinical oncology, chemistry and pharmacology.

Through this funding, it is hoped that new insights will be gained that can be translated into clinical interventions that will improve treatment outcomes and quality of life for patients with advanced cancer.



Identify and target dormant cancer cells

CONTEXT

Cancer cell dormancy is a process whereby cells enter a reversible cell cycle arrest. Dormant cells are considered to be responsible for metastatic relapse. Disseminated cancer cells can persist in a dormant state for many years or decades following treatment, but in response to signals that have not yet been fully identified, such dormant cells can reawaken and grow into larger metastatic lesions. The ability to identify and characterise cancer cells in a dormant state is challenging, but this is key to gaining a better understanding of the signals and environment that allows the establishment of dormancy and how dormant cells are reactivated. Such understanding would enable novel approaches to target dormant cells by preventing reactivation or enabling selective eradication.

BARRIERS AND OPPORTUNITIES

This challenge specifically relates to the study of dormant cells that exist after seemingly successful treatment (i.e., following a latent period where the patient displays no clinical symptoms). The goal is to understand the molecular mechanisms that regulate the dormant state and use this understanding to develop therapeutic strategies.

Examples of the types of questions that could be addressed in this challenge include but are not limited to:

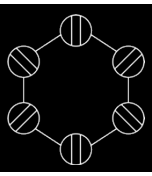
- Can methods be developed to detect and isolate dormant cells?
- Can we identify circulating biomarkers that indicate the presence of dormant cells?
- What role does the microenvironment play in regulating the dormant state?
- Is it possible to develop preclinical models that accurately reflect tumour dormancy in patients and provide novel insights into how dormancy is regulated?
- By understanding the mechanisms regulating tumour dormancy, can we develop approaches to eradicate dormant cells, or prevent their re-emergence?

VISION AND IMPACT

The goal of this challenge is to develop innovative approaches to accurately study dormant tumour cells and better understand the mechanisms that control dormancy in patients. Eliminating dormant tumour cells or preventing their activation has huge therapeutic potential to limit the rates of cancer recurrence.

Addressing this challenge will require a multidisciplinary team, which may include expertise in biology, mouse modelling, and clinical oncology to overcome the barriers of how to identify and isolate dormant

cells. Teams will have to develop relevant experimental models to allow detailed consideration of both tumour intrinsic and extrinsic factors that regulate dormant cell behaviour, studies should also be extended into human systems.



Understand the biology of ecDNA generation and action, and develop approaches to target these mechanisms in cancer

CONTEXT

Extrachromosomal DNA (ecDNA) is increasingly recognised as a potent source of driver oncogene copy number amplification events in human tumours. ecDNAs have been found to be associated with hijacked enhancer elements, driving the expression of multiple oncogenes simultaneously and are likely sources of tumour heterogeneity, drug resistance and cell fitness. Reintegration of ecDNA intrachromosomally, within homogeneously staining regions and unequal distribution of ecDNAs at cell division to daughter cells presents challenges to their detection and control.

Relatively little is known about the origins, evolution, genomic organisation or clinical impact of ecDNA. Tools now exist to infer their sequence, structure and regulation that when combined with advances in ecDNA biology in prokaryotes and lower eukaryotic cells, would allow a greater understanding of therapeutic vulnerabilities in intractable cancers.

BARRIERS AND OPPORTUNITIES

Little is known about the genomic organisation or mechanisms that drive ecDNA formation or reintegration in cancer that could be targetable. However, research over the last 50 years in both eukaryotes and prokaryotes has revealed the role of ecDNA in immune evasion (bacteria) and in ageing, chromosome evolution and genome instability.

Current short read sequencing platforms render the detection and inference of ecDNA challenging. Therefore, optimising ecDNA purification and enrichment approaches, sequencing technologies and informatics tools will be important. The absence of centromeres results in unpredictable segregation of ecDNA at mitosis, challenging our evolutionary thinking in cancer. The impact of such non-mendelian patterns of inheritance have not been modelled or studied in depth in cancer.

Driver "undruggable" oncogenic events such as N-Myc are subject to ecDNA driven amplifications and drug resistance enzymes may be transiently fuelled by such events. Understanding ecDNA evolution and their conserved patterns of organisation could inform wider knowledge of genome organisation, enhancer activity and the role of epigenetic regulators in controlling genome stability. For example, histone methyltransferases implicated in their generation, are now eminently targetable.

Examples of the types of questions that could be addressed in this challenge include but are not limited to:

- What is the biological mechanism(s) involved in the generation of ecDNA?
- What is the role of ecDNA in oncogenesis?
- Are there targetable vulnerabilities to ecDNA-driven cancers that could be exploited for treatment?

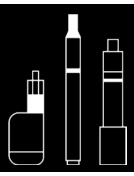
- Can we model and predict ecDNA evolution?
- Are there therapeutic targets that would eliminate ecDNA? Stop its integration into chromosomal DNA? Or block its re-emergence from genomic integration?

VISION AND IMPACT

This challenge should synthesise our understanding of conserved patterns of ecDNA genomic organisation and drive discoveries into their regulation, evolution and re-integration. This could provide new therapeutic targets to maintain genome stability in cancer.

A multidisciplinary team will be required to address this challenge, which could coalesce the fields of cellular and evolutionary biology, cancer genomics, drug discovery and development, and computational modelling to understand how ecDNA structures form and how they could be limited.

Knowledge gained from this challenge could provide tractable therapeutic approaches to undruggable oncogenes (e.g. MYC), limit the over-expression of multiple oncogenes simultaneously and prevent the rapid acquisition of drug resistance through metabolic enzyme overexpression.



Determine the potential benefits and risks of e-cigarette use

CONTEXT

It is estimated that tobacco smoke causes more than 20% of cancer deaths worldwide. Despite significant health warnings and efforts to reduce the number of people smoking, if current trends of tobacco use continue, it is predicted that it will result in 1 billion deaths in the 21st century.

Smoking cessation is the process of stopping tobacco smoking. This involves both reducing the proportion of younger people who start to smoke and increasing the proportion of established smokers who quit. Nicotine replacement therapies have been an important part of smoking cessation programmes. In the last decade, e-cigarettes, devices that deliver nicotine in the form of a vapour inhaled into the lungs without burning tobacco, have become widely popular. Randomised trials have indicated that e-cigarettes can assist some smokers in quitting, but it is unclear how effective they are for long term smoking cessation. In addition, the full extent of both the short and long-term health risks for e-cigarette users has yet to be fully determined, and the impact at a population level remains uncertain.

Conflict-of-interest free research needs to be accomplished to understand the potential benefits and risks of e-cigarettes at a global scale.

BARRIERS AND OPPORTUNITIES

Cancer organisations, health systems and regulators urgently need to know the risks and benefits of e-cigarettes. These could be impacted by multiple factors, and questions that could be addressed range from the patho-physiological impact to the societal implications of e-cigarette smoking. This may include but would not be limited to:

- How safe are e-cigarettes, and are there long-term health consequences? Can we understand the toxicology of e-cigarettes, the effects of nicotine on the developing and adult brain, on respiratory and cardiovascular health and other health metrics in established e-cigarette users?
- Do e-cigarettes enable a reduction in tobacco smoking when accounting for use at the population level taking into account increased uptake amongst teenagers and young adults?
- How do consumer preferences, such as delivery systems, nicotine content, and flavours alter the potential long-term effectiveness of e-cigarettes? Note, this should not include studies on cannabidiol (CBD) or tetrahydrocannabinol (THC).
- Can we analyse the effectiveness of regulation of e-cigarettes? How effective are e-cigarettes for long-term smoking cessation?

- What are the social implications of wide-spread e-cigarette use?

VISION AND IMPACT

At present, research in the field is fragmented and mostly small-scale. Multinational and truly multidisciplinary proposals are needed. Success in this challenge would be to generate evidence that could inform objective, high-quality information on the potential benefits and risks of e-cigarette use for established smokers who wish to quit smoking, and the general public.

This challenge aims to bring together disciplines such as pharmacology, molecular toxicology, molecular biology, immunology, epidemiology, behavioural science, law and health policy to address this issue.

Determine how inflammation causes cancer

CONTEXT

It is estimated that up to 50% of human cancer is caused by definable risk factors that could be avoided. When the steps that arise from exposure to a risk factor to cancer initiation are known, for example following exposure to UV or to tobacco smoke, this knowledge has been very important for prevention, diagnosis, and in some cases therapeutic intervention.

Inflammation is one of the most common biological stages following exposure to potential carcinogenic agents or conditions. Inflammation is characterised by a large number of cellular changes, and it is not known whether there are different functional subclasses of inflammation. Importantly, we do not know which of the many changes seen in inflammation are essential for increasing cancer risk. Identifying the critical steps that lead from inflammation to cancer initiation could provide points for cancer prevention and important markers for diagnosis of early stage cancer.

BARRIERS AND OPPORTUNITIES

While inflammation is commonly reported in many biological conditions, the molecular characteristics that are directly causal for cancer initiation remain unclear. Inflammation frequently sets up oxidative conditions which can damage DNA, proteins, and lipids. Inflammation in some settings will stimulate repeated cell division with the associated potential for DNA mutation. Inflammatory conditions induce many changes in transcriptional programmes. In addition, increasing evidence points to immune dysfunction with ageing. Any of these or other associated changes could be integral for cancer initiation.

Teams will need to establish reproducible systems to induce inflammatory conditions that allow examination of characteristic changes as well as the ensuing recognisable stages of early cancer development. Variations in the types of inflammatory stimuli and the influence of ageing upon the immune response should be considered. These systems will need to represent various human tumour development settings and should correlate with changes seen in various tissue environments.

Successful teams will need to understand which of the changes seen in various precancerous lesions are key to the inflammatory process. Functional tests will be required to determine which of these changes are essential for subsequent steps in tumour development. It will be essential to determine whether there are recognisable downstream events emanating from inflammatory conditions that are required for cancer initiation.

Important questions that might be considered include but are not limited to:

- Do inflammatory markers change by tissue source or type of upstream stimulus?
- What is the timing of inflammation with unstoppable tumour initiation?

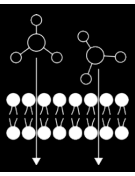
- Is there more than one type of inflammation?
- Can specific components of the inflammatory state be markers for the rate or severity of tumour development?
- How does the quality and potency of the immune response alter with ageing?

VISION AND IMPACT

Success in answering this challenge would be to identify the causative events associated with inflammation that lead to cancer development in vivo. This could lead to new targets for cancer prevention or better use of existing interventions. Better systemic biomarkers could advance the diagnosis of early stages of cancer development or warn individuals of potentially dangerous advancing conditions.

To address this challenge will require a multidisciplinary team that may include epidemiology and cancer biology expertise.

Deeper understanding of how dangerous risk factors lead to cancer initiation will help us understand how this important but still mostly mysterious stage of cancer development occurs.



Systemically deliver macromolecules to intracellular targets for therapeutic benefit in cancer

CONTEXT

In recent years, scientists have been experimenting with 'macromolecules' to target and destroy cancer cells. A macromolecule is defined as any very large molecule, with a molecular weight exceeding about 1,500 Daltons. These macromolecules can disrupt the processes that cancer cells use to survive, for example by stopping them from growing or by flagging their presence to the body's immune system. Importantly, they can be engineered to be far more specific and active than current small molecule therapies.

This approach is often effective on cancer cells in the laboratory, but unlike conventional 'small molecule' treatments, it is difficult to deliver these macromolecules systemically to the inside of cells where they need to act and engage with their target.

If we could develop approaches to deliver these macromolecules to any and every cell in the body, including the central nervous system, ensuring they crossed the cell membrane and engaged with their target, it would create new ways to treat cancer and could also have a significant impact on other diseases.

BARRIERS AND OPPORTUNITIES

The exact barrier in delivering macromolecules is crossing the cell membrane to enter the cytoplasm and nucleoplasm where target molecules reside. Many molecules that bind to the cell surface enter endosomes but cannot escape that membrane compartment. Bacterial protein toxins have evolved mechanisms of endosomal escape and certain macromolecules, such as cyclosporin, have an intrinsic ability to cross membranes. Viruses can deliver both DNA and RNA into the cell, providing a precedent for an intractable problem. New approaches to tackle this challenge could involve:

- The use of novel nanoparticles that mimic viruses
- Engineered proteins that use toxin like mechanisms
- Exploiting a deep understanding of the design principles that allow certain macrocyclic peptides to cross the membrane by passive diffusion

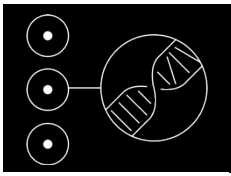
It will also be important to measure target engagement as part of this challenge, so developing suitable assay systems and potent metabolically stable macromolecules will also be required.

Approaches should be practical, affordable and innovative around cellular mechanisms of uptake that can be developed for use in humans.

VISION AND IMPACT

Success in answering this challenge would be the demonstration of efficient cellular entry and target engagement of a number of macromolecules in animal models. It would be desirable to demonstrate that the approach worked for multiple targets e.g. Myc, Ras, Mdm2, EWS-Fli1. Ultimately, a universal delivery system for macromolecules would be transformative allowing thousands of new targets to become "druggable "and improving outcome for cancer patients.

Addressing this challenge will require a multidisciplinary team, which may include expertise in material science, membrane chemistry, virology, microbiology, molecular cell biology and pharmacology.



Understand how cells and tissues maintain "normal" phenotypes whilst harbouring oncogenic mutations and how they transition to become a tumour

CONTEXT

Recent studies looking at normal tissues from different anatomical sites have revealed that cells frequently harbour somatic mutations. These cells and tissues appear to be phenotypically normal, but surprisingly some of them carry known cancer mutations (e.g., mutant RAS or p53 loss). The selection and clonal expansion of cells containing driver mutations seems to be a feature of normal ageing. Identification of these cells has opened the opportunity to understand how they and their resident tissues retain a normal phenotype. In addition, their discovery raises questions about what changes are needed promote tumour development following these initial mutations. This challenge focuses on how cell physiology is changed by the presence of one or more cancer mutations and asks what types of genetic or environmental changes allow these cells to progress to early stage tumours.

BARRIERS AND OPPORTUNITIES

To date, work in model systems has suggested that acquisition of a relatively limited number of mutations in key cancer driver genes is sufficient to transform a normal cell into a cancer cell. However, recent observations confirm that the situation is more complex in tissues and raises interesting and important questions about how tumour progression is limited or suppressed. The challenge is to understand the behaviour and selection of cells harbouring oncogenic mutations, when they remain normal and if, where, and how they undergo tumorigenic progression. This challenge should focus beyond cell intrinsic factors alone and should explore the role of the surrounding cells or stroma, including the extracellular matrix, and the role of the host in restraining progression. Considerations should include the influence of the tissue and organ, and/or any systemic systems, such as the immune system, metabolite availability or infection. Teams should identify the mechanisms that allow these cells to remain normal and identify the molecular events that are necessary to allow these cells to progress to malignancy. Other areas that could also be addressed include but are not limited to:

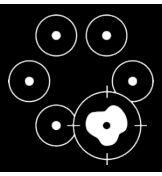
- Do any "normal" somatic cells contain combinations of oncogenic events known to drive tumorigenesis (e.g., Kras mutations plus loss of p53) or does each cell harbour only one of these events?
- How many different types of mechanisms allow cells to progress from carrying one oncogenic mutation to tumour formation?
- How do processes such as inflammation, wound healing, or tissue regeneration impact the behaviour of these cells? What are the critical mechanisms underlying such interactions?
- How do these processes relate to the action of tumour promoting agents?

- What is the impact of ageing on the mechanisms that restrain these cells?
- What is the role of genomic stability and lack of chromosomal rearrangements and copy number changes in maintaining a normal phenotype?
- Are there oncogenic alterations that never occur in normal cells (e.g., TERT promoter alterations)?
- Does the order of acquisition of mutations make a difference to the outcome?
- What impact will these cells (especially considering their increased abundance with age) have on cfDNA approaches for early diagnosis?
- Is there a link between more or larger clones of such cells and increased cancer risk?

VISION AND IMPACT

This challenge seeks to expand our understanding of the cell intrinsic and extrinsic mechanisms that exist to prevent malignant progression and to identify the steps that allow early tumour development. The challenge asks that teams look beyond the simple accumulation of mutations and understand in molecular detail how a normal cell harbouring a cancer mutation is restrained from oncogenic progression and then identify the critical steps for progression at the earliest steps of tumour development. Addressing this challenge will require a multidisciplinary team, which could bring together expertise in genetics and evolutionary biology, with functional analyses of both individual cell behaviour and cell-cell, cell-host interactions, human tissue developmental biology, tissue and cell imaging, mechanistic cell biology, mouse model development, and systems biology.

Knowledge generated in this challenge could help identify key and potentially targetable steps in the development of cancer.



Understand and exploit senescence to improve cancer treatment

CONTEXT

Senescence is an effective endogenous anti-cancer mechanism, e.g., BRAF mutated induced senescence in melanocytes in naevi. Much of the research on senescence is carried out in non-malignant primary cells, but evidence suggests that cancer cells can still enter senescence. One of the shared properties of senescent cells is the Senescence Associated Secretory Phenotype (SASP), which leads to a local inflammatory response. The altered cellular state of the senescent cell in terms of gene expression, metabolism and chromatin state offers potential opportunities to selectively eradicate senescent cancer cells (senolysis). The challenge is to induce senescence in cancer cells and identify ways to selectively kill the senescent cancer cells.

BARRIERS AND OPPORTUNITIES

A major barrier in the field is that there is not a gold standard biomarker of the senescent state, certainly not in cancer cells. There is an urgent need to identify reliable biomarkers that identify senescent cancer cells. This will enable high throughput technologies to identify genes and compounds that effectively induce senescence in cancer cells. Senescence has not yet been used as a read out in compound screens by the pharmaceutical industry, and hence, has been missed in short-term read outs in large drug screens.

Another barrier is that the few available senolytic compounds have context dependence, which limits their use. It will be important to identify common vulnerabilities of senescent cancer cells that can be used for their ablation. Ablation of senescent cells may also take advantage of the SASP produced by senescent cancer cells, e.g., by combinations with immuno-oncology approaches.

Ablation of senescent normal cells may also be considered as a way to reduce the side-effects of chemotherapy in patients.

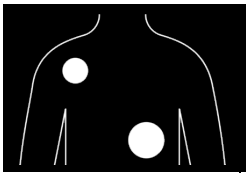
Examples of the types of questions that could be addressed in this challenge include but are not limited to:

- What are the common vulnerabilities of senescent cancer cells and how could these features be targeted?
- Can we develop novel or more effective approaches to effectively induce senescence in cancer cells?
- What is the best approach to remove senescent cells?
- What is the physiological impact of inducing senescence and/ or removing senescent cells more widely in the context of tumour development?

VISION AND IMPACT

This challenge invites innovative approaches to identify novel compounds and targets that either induce senescence in cancer cells and/or approaches that can be used to kill senescent cancer cells. Validation of the identified compounds and targets in appropriate immunocompetent animal models will be instrumental for validation of the proposed therapies.

To address this challenge, a multidisciplinary team will be required, bringing together researchers from disciplines such as biology, chemistry, drug discovery, pharmacology and clinical oncology. Ideally, the challenge should culminate in a proof of concept clinical study to demonstrate the utility of the approach in patients.



Develop novel therapies to target unique features in solid tumours in children

CONTEXT

Cancer is a leading cause of death by disease in children globally, and progress in the treatment of children with solid tumours, which includes brain tumours, has stalled. For those children who relapse, there are fewer treatment options available, meaning the outlook is often poor, and outcomes for some paediatric cancers have not improved in more than 30 years.

Despite advances in understanding the biology of some paediatric cancers, standard curative treatment regimens rely primarily on cytotoxic agents, developed decades ago, and radiotherapy. Such therapies induce severe late, long-term effects, including second malignancies, cardiac, neurologic and skeletal toxicity, and infertility.

BARRIERS AND OPPORTUNITIES

Tumours arising in children are fundamentally distinct from those that occur in adults as they often represent disordered development of embryonal tissues. While many fundamental pathways that drive oncogenesis in paediatric solid tumours, including brain tumours, have been defined, effective targeted therapeutics have not been developed.

This is in part because the known oncogenic targets in children's solid tumours characteristically involve mutated or overexpressed transcription factors and/ or epigenetic proteins, which are largely considered "undruggable". In addition to the challenge surrounding drug development, there has also been a lack of focus on paediatric solid tumours compared to adult cancers by the biotechnology and pharmaceutical industries, due to the small market size.

Examples of the types of questions that could be addressed in this challenge include but are not limited to:

- Can we develop a deeper understanding of the biology of children's solid tumours to identify the best approach to develop novel therapies that target their unique biological features, e.g. mutant oncoproteins or transcription factors?
- Can immunotherapeutic approaches be developed which are effective in the paediatric solid tumour setting?

VISION AND IMPACT

Although there are some large-scale initiatives in this area, research is often fragmented. Therefore, multinational and truly multidisciplinary, disruptive proposals are needed.

This challenge aims to bring together multidisciplinary teams that could include cancer biologists, developmental biologists, clinical investigators, animal modellers, medicinal chemists and immunologists.

A successful application will discover, develop and optimise novel therapeutic(s) and launch early phase testing in small clinical trial(s) that incorporate relevant pharmacokinetic and biologic endpoints to understand the basis for success or failure of the therapy.

Development of effective targeted therapeutics for paediatric solid tumours will improve survival for children diagnosed with cancer and will diminish the lifelong toxicities often experienced by survivors of these diseases.