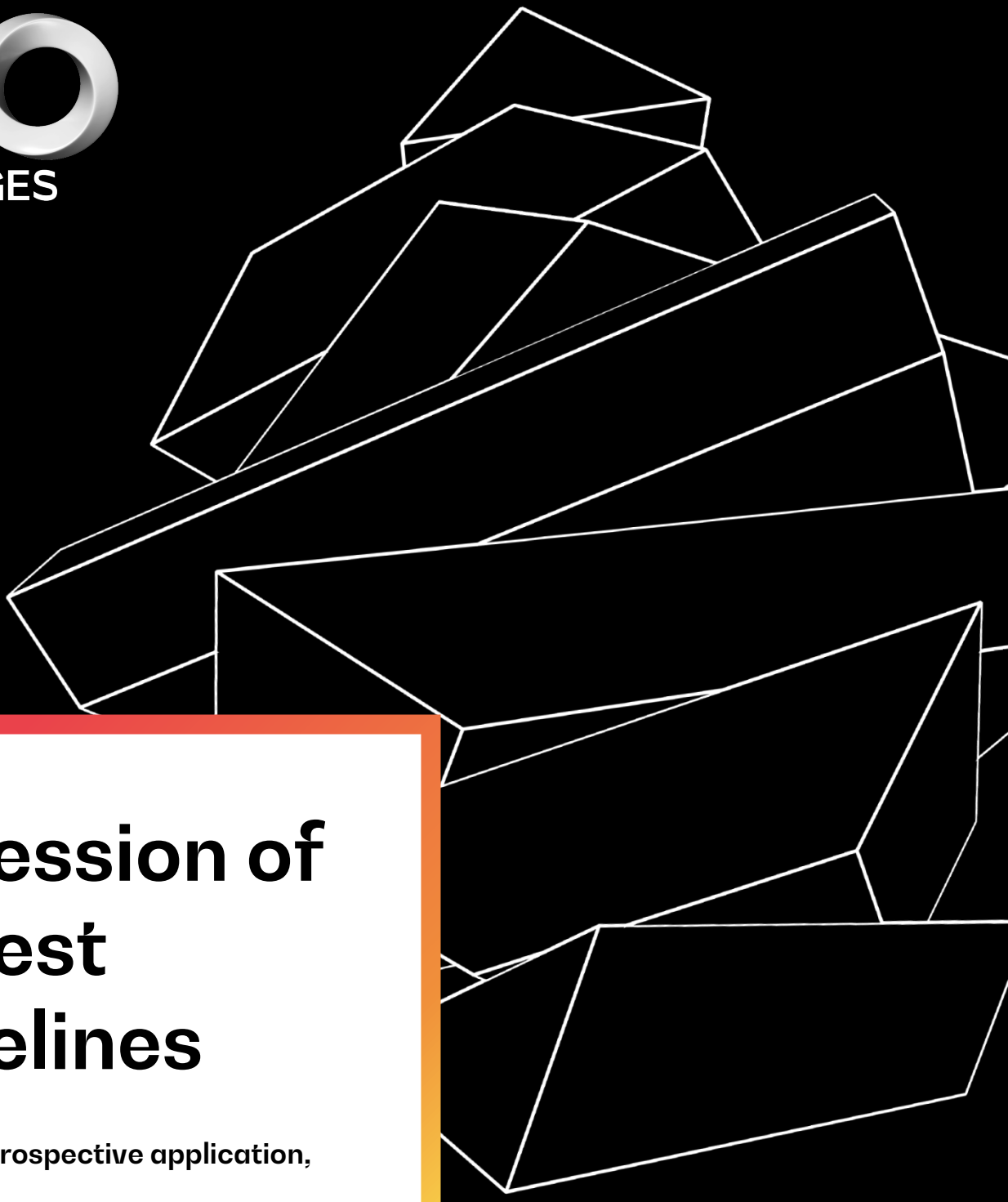
CANCER GRAND CHALLENGES



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

Contents

1. Summary of key dates

1. Complete questionnaire	2. Submit EOI	3. Shortlisting	4. Submit full application	5. Award starts
15 June 2023	22 June 2023	July 2023	26 October 2023	2024

1. Complete pre-submission questionnaire

Once you have read our new set of cancer grand challenges and decided you'll put together a team to apply to tackle one of them, you'll need to 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. Submit your Expression of Interest

Assuming the office doesn't have any questions about your answers, we'll open an application form, which you should complete in line with these guidelines.

3. Committee shortlists teams

The Cancer Grand Challenges Scientific Committee (CGCSC) will recommend which EOIs should be shortlisted. Shortlisted teams will receive feedback from the CGCSC on their proposals, as well as from the Cancer Grand Challenges Advocacy Panel (CGCAP) on how they plan to involve and engage patients and the public with their proposed research. It won't be possible to provide all unsuccessful teams with feedback.

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

4. Full application and interview

Shortlisted teams will submit a full application and attend an interview with the CGCSC on 11-13 December 2023. The CGCSC will recommend which teams should be funded.

5. Award

Winning team members will 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

Addressing the obstacles that continue to impede progress in cancer research

Cancer Grand Challenges supports a global community of world-class research teams to come together, think differently and take on some of cancer's toughest challenges.

These challenges continue to impede research progress, and no one scientist, institution or country will be able to solve them alone. Cancer Grand Challenges teams are empowered to transcend the traditional boundaries of geography and discipline, and ultimately change outcomes for people with cancer.

The toughest challenges in cancer research

Cancer Grand Challenges works with the global research community and people affected by cancer to identify the toughest challenges in cancer research, then dares interdisciplinary, world-class teams to take them on. Our research teams are currently tackling 10 of cancer's toughest challenges. We've also announced nine ambitious new challenges – see Appendix 1.

Founded by the two largest funders of cancer research in the world – Cancer Research UK and the National Cancer Institute in the US – and uniting an international community of partners, Cancer Grand Challenges aims to make urgently needed progress 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 problems. Cancer Grand Challenges awards are not intended to fund research that would be fundable by other response-mode schemes and initiatives.

The Cancer Grand Challenges initiative supports teams involving 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. Teams will involve individuals with the potential to become future leaders in cancer research, as well as people affected by cancer to support efforts to ensure the needs of patients are heard and understood.

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:

- **Quality**: the work proposed must be of the highest international scientific calibre, advancing a robust and unbiased approach to accomplishing its goals.
- **Relevance**: there must be a clear plan to address the challenge as it has been articulated. The research plan should address the challenge in a way that fully takes advantage of the opportunity to pursue a large, coordinated, international team-based effort. The application should describe how successfully completing the proposed work has the potential to change our understanding of the concepts, methods, technologies, treatments, services, and/or interventions associated with the challenge and related scientific fields.
- **Innovation**: the work must involve the development of new methodologies, approaches, theoretical concepts, instrumentation, resources and/or capabilities to tackle the challenge in a novel way. Rather than scaling up existing experimental approaches, the application should describe how the scope and scale of the research will allow for unique and innovative approaches that are not otherwise possible via other funding mechanisms.

- **Team**: the very best team should be assembled to address the challenge. The team must
  - Comprise a diverse group of investigators, each of whom has a demonstrated record of accomplishments in advancing their respective fields;
  - Be interdisciplinary, drawing on researchers with complementary and integrated expertise, and attracting new thinking to cancer research;
  - Be international, facilitating global collaboration between researchers;
  - Incorporate training for future leaders in cancer research;
  - Demonstrate an ability to operate as a highly functional research team, with maximum cohesion and collaboration.
  - Be led and organised in such a way that is appropriate to achieve the team's scientific objectives.
- **Impact**: the ambition must be that the results of the proposed research could have significant benefit for patients and/or the wider public in the long term.

4. Challenge teams

Applicants should carefully consider the most appropriate make-up for their team and how it will be structured and managed. Teams must 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.

At EOI stage, we expect a team to include one Team Lead (TL – see section 4.1) and multiple Co-Investigators (Co-Is – see section 4.2). Applications are welcomed from teams working across a breadth of disciplines, including but not limited to: the biomedical sciences; software development and technology; engineering and physical sciences; and 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 in any capacity (i.e. as TL, co-I or as a collaborator); other researchers from their host institutions can apply.

If shortlisted, teams will be required to recruit an appropriate team of patient advocates (see section 4.4). They will also be strongly encouraged to recruit a part-time programme manager (see section 4.5); appointment of a full-time programme manager is a requirement of funded teams.

4.1. Team Lead

Each team must have one Team Lead, who will be the person responsible for the overall scientific and technical direction of the team, as well as being the lead administrative contact.

It is recommended that the team should have only one TL. If the team wishes to include multiple TLs, a strong justification should be included in the 'Rationale for team make-up' section of the EOI form (see section 7.4). Any individual named as a TL will be expected to spend a significant proportion of their research time (25% minimum effort) on the Cancer Grand Challenges award.

The TL 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.

TLs cannot be named as TL on more than one EOI, but may be named as a Co-I on (an)other EOI(s). Similarly, TLs of existing Cancer Grand Challenges team may not lead new applications, but can participate as Co-Is.

4.2. Co-Investigators

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

It is expected that all Co-Is will receive significant funding in order for them to make a substantial contribution to a team. It is therefore generally recommended that teams include no more than 10 Co-Is in their application. If a team wishes to include a higher number of Co-Is, this should be clearly justified in the in the 'Rationale for team make-up' section of the EOI form (see section 7.4). As a guide, Co-Is should expect to contribute at least 10% effort to the award.Commercial collaborations with the academic components of a CGC team 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, and will be signatories to the Cancer Grand Challenges Award Agreement (see section 5) if funded.

4.3. Collaborators

Academic or commercial collaborations beyond the funded team are encouraged. You do not need to have identified these at EOI stage, 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. Meaningful and impactful patient advocate involvement and engagement ensures patients' needs are always at the heart of research, and funded teams are expected to meaningfully consult, collaborate and partner with patient advocates wherever such interaction can add clear value and accelerate progress.

If shortlisted, teams will be expected to recruit an appropriate team of patient advocates with clearly defined roles and remits. Patient advocates should aim to represent people affected by cancer at large and not provide just their individual viewpoint or that of any advocacy organisation. Patient advocates will work with TLs and Co-Is to develop detailed involvement and engagement plans for their teams. They will then be critical in delivering and implementing these plans. For more information about the role of patient advocates and about building your advocacy section, please refer to our additional information about patient advocate involvement and engagement.

4.5. Programme manager

Shortlisted teams are strongly encouraged, and funded teams are required, to recruit a programme manager to coordinate the research consortium, with responsibilities which could include, but aren't limited to:

- Assisting the CGC TL and Co-Is in monitoring and ensuring team compliance with CRUK and NCI award requirements;
- Ensuring 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 meetings;
- Coordinating with, as well as ensuring information is disseminated to and collected from, relevant contacts (e.g. research, finance, technology transfer) at participating institutions.

Programme managers should have experience managing large, 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.

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

Cancer Grand Challenges funding is subject to Terms and Conditions, and policies, set out in a series of documents, all of which are available on our website:

- **Cancer Grand Challenges Award Agreement** – setting out participants' contractual obligations and signed by authorised representatives of Cancer Research UK, NCI and all participating institutions in a team;
- **Cancer Grand Challenges Award Management and Funding Policy Guide** – detailing expectations of the management of Cancer Grand Challenges funding and relevant policies, incorporated by reference in the Award Agreement;
- **NCI Cancer Grand Challenges OT Policy Guide** – providing supplementary policy information on behalf of NCI;
- **Cancer Grand Challenges Commercialisation Policy** – setting out how any opportunities for the commercialisation of research results will be handled;
- **Cancer Research UK Cancer Grand Challenges Allowable Costs Guidance** – detailing specific expenditure that may or may not be charged to the Cancer Research UK component of a Cancer Grand Challenges award.

Teams are encouraged to familiarise themselves with these documents at the earliest possible juncture, and to disseminate them to their fellow researchers and host institutions. Members of Cancer Research UK and NCI staff will meet with shortlisted teams to address any questions they may have.

5.1. Publicity

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.

5.2. 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 TL 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

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.

At EOI stage, teams are required to provide an approximate breakdown of their proposed costs against each work package over the lifetime of the award (as detailed in section 7.4).

If funded, 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 through a Grant Award Letter; ~50% will be issued in US dollars (USD) by NCI through a Notice of Award.

6.1. Indirect costs

In some cases, 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.

Cancer Research UK and NCI will consider supporting indirect costs as a proportion of their individual contributions to the direct costs at each institution as follows:

Funder	Institutions in the UK	Institutions in the US	All other institutions
Cancer Research UK	None	10%	Up to 10%, only in jurisdictions where indirect costs are typically funded through charitable or public research grant funding*
NCI	8%	Using the institution's federally negotiated indirect cost rate†	None

* Most European countries do not use this funding model and so indirect costs would not be paid.

† 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.

Neither funder will support indirect costs for commercial entities.

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 not used Flexi-Grant (or Cancer Research UK's old system, eGMS), you will need to:

- Visit cancerresearchuk.flexigrant.com
- Click 'Register' and follow the onscreen instructions.

Once you have logged into Flexi-Grant, you will not find the option to begin an EOI for Cancer Grand Challenges on the 'Start application' page. A form can only be opened once you have completed the following step. For help using Flexi-Grant, contact us using the details in section 8.

7.2. Pre-submission questionnaire

Before we can give you access to an EOI form on Flexi-Grant, the TL must submit a short questionnaire to the office. The information provided will be used to check eligibility against the criteria set out in sections 3 and 4 of these guidelines, and won't be disclosed to the CGCSC as part of the 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.

We aim to process questionnaires within two working days, but lead times may be slightly longer in the event of a high volume of queries. The deadline for submission is 15 June 2023, one week in advance of the EOI deadline.

7.3. Expression of Interest

Assuming there are no questions about the answers given in your pre-submission questionnaire, you will receive an email letting you know that an EOI application form is open on Flexi-Grant. The deadline for EOIs is 22 June 2023.

You will be required to provide the following:

- A publishable research abstract (this may be used on our website, to help Cancer Research UK in fundraising activities and for other purposes so should not include any confidential information).
- A completed EOI template (see section 7.4);
- A completed biosketch template for the TL and all Co-Is (see section 7.5).

7.4. Expression of Interest template

Download the EOI template from Flexi-Grant, and complete the sections per the table below.

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, discussing specific technologies and methodologies that will be employed.

Section of EOI template	What it should cover	Word count
Team	List of team members	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	1,000 words
Patient advocate involvement and engagement	Description of your commitment to how you will involve people affected by cancer in your scientific programme; and how you will engage the public with your research (see section 4.4).	300 words
Financial overview	Predicted spend for each work package, over the award in pounds sterling (GBP) Any capital requests in excess of 5% of the likely total award spend	n/a

7.5. Biosketches

Download the biosketch template from Flexi-Grant, and include a completed copy for the TL and all Co-Is per the table below. 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. Feedback

Shortlisted teams will receive feedback on their proposals following the CGCSC review. This feedback will be shared by the office; CGCSC members are not permitted to speak to team members about their applications directly. Shortlisted teams will also receive advice and feedback from the CGCAP about their patient advocate involvement and engagement plans.

Due to the large volume of EOIs anticipated, unsuccessful applicants are unlikely to receive feedback on their proposals.

8. Contact details

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

Appendix 1: The challenges

Decipher the functional basis underlying the association between ageing somatic tissues and cancer

CONTEXT

Cancer incidence increases dramatically with age and is the leading cause of death in both males and females aged 60-79 years old. Ageing is associated with tissue remodelling and an accumulation of somatic mutations, genome instability, epigenetic alterations, and mitochondrial dysfunction amongst other cellular abnormalities. How distinct ageing processes increase cancer risk at different organ sites remains unclear. No single cellular process associated with an ageing soma sufficiently explains cancer risk across all tissues.

This challenge seeks to understand how ageing-associated molecular changes in somatic cells and immune dysfunction together with endogenous and exogenous environmental factors, impact early cancer initiation in ageing somatic tissues, and organ-specific cancer risk.

BARRIERS AND OPPORTUNITIES

Ageing is associated with multiple aberrations in cellular physiology, immune dysfunction, tissue homeostasis and architecture. Somatic cell dysfunction with age is manifested by genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, altered intercellular communication and stem cell exhaustion. Ageing tissues suffer from extracellular matrix remodelling (ECM) that might permit expansion of mutant clones within normal tissue and an ageing immune system impairs immune surveillance.

No single ageing process explains cancer risk across all tissues suggesting that distinct cellular processes associated with ageing drive cancer risk in different tissues. The multi-faceted impact of ageing on cellular and organ function, the absence of tractable model systems that reflect human longevity and our nascent understanding of clonal evolution of normal cells in ageing tissue and the impact of ageing processes on tissue architecture have together limited our understanding of how ageing increases cancer risk.

New approaches are required to:

- Develop functional insights into how ageing contributes to cancer risk

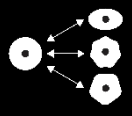
- Understand how changes in tissue architecture driven by ageing and prolonged exposures to environmental stimuli might alter clonal dynamics in normal tissue and influence cancer risk
- Understand how distinct ageing-associated cellular and immune processes impact early cancer initiation and organ-specific cancer risk

VISION AND IMPACT

Addressing this challenge would provide a deep functional understanding of diverse cellular and immune ageing processes and their functional consequences on organ-specific cancer risk.

Techniques could be developed to understand how alterations in the ECM constrain or promote clonal expansions within normal tissue and how ageing of somatic cells, taking into account environmental exposures, contributes to tumour initiation and promotion. Addressing this challenge will require an interdisciplinary team that could include members with expertise in ageing syndromes and animal modelling, natural ageing processes in human tissue, cellular senescence and mitochondrial function, immunology, extracellular matrix biology, environmental carcinogenesis, and clonal evolution of normal tissue. Applicants should specify their definition of ageing as it relates to the proposed studies, including a rationale for the models selected and/or age range of study participants.

By identifying functional ageing processes driving organ-specific cancer risk, new interventions that lower cancer risk in ageing populations could be developed.



Understand cancer cell plasticity and its contribution to the development of pan-therapeutic resistance in cancer

CONTEXT

Cancer cells show remarkable plasticity in which they can switch lineage and activate latent differentiation programmes, yet the principles governing plasticity in cancer cells remain poorly understood. This plasticity may allow cancer cells to develop stem-like properties, drive invasiveness and metastasis and to evade therapy by developing broad resistance to radiotherapy and cytotoxic chemotherapy.

Increased understanding of cell fate determination through epigenetic reprogramming means that it is timely to study in detail how cancer cells achieve these switching processes. Advanced sequencing technologies are also now available to interrogate single cells and clonal populations. Blocking or exploiting such switching processes could inhibit the recurrence of cancer and eliminate resistant cells after successful primary treatment.

BARRIERS AND OPPORTUNITIES

Cancer initiation, invasiveness and metastases likely involve profound alterations in the epigenetic state of cells during clonal evolution. Furthermore, many cancers progress or recur despite an initial response to treatment. The progressing or recurring cancer is then often more resistant to therapeutic intervention. The basis of these phenomena result, in part, from the plasticity of cancer cells which allows them to adopt new cellular programmes. Understanding of how epigenetic diversity arises and how distinct epigenetic states functionally influence cancer evolution and drug resistance would allow the development of novel approaches to inhibit or exploit plasticity for improved treatment.

There is a need to understand how cancer cells adopt different states including the epigenetic and transcriptomic mechanisms involved and the role of the tumour microenvironment (e.g., mechanical stresses, immune system) in influencing plasticity.

This challenge calls for bold new approaches to understand cell plasticity, which might include:

- Single cell analysis of phenotypic variants of clonal cancers to understand the transcriptional and epigenetic changes associated with plasticity
- Investigating the role of cytogenetic alterations and genome duplication
- Examining the potential role for cell fusion in plasticity

- Development of biomarkers that allow the determination of plasticity in tumour material

VISION AND IMPACT

This challenge seeks to expand our knowledge of the developmental switching programmes of cancer cells, how they contribute to cancer progression and what mechanisms, epigenetic or otherwise, govern them. Potentially regulating these programmes could improve the effectiveness of current therapies or offer new non-toxic alternatives, for example differentiation therapies leading to novel combination regimens.

This challenge will require an interdisciplinary team which could include pathologists, molecular biologists, cell biologists, computational modellers, evolutionary biologists, mathematicians, and pharmacologists.

By addressing this challenge new insights into these complex processes will be gleaned, potentially leading to improved patient survival.

Understand the mechanisms through which genetics, biology, and social determinants affect cancer risk and outcomes in diverse populations, to motivate interventions to reduce cancer inequities

CONTEXT

Inequities in cancer prevention, screening, and treatment lead to disparities in cancer incidence and mortality and are a major public health concern.

The causes of cancer inequities are complex yet often poorly elucidated. While most inequities are the consequences of social determinants and circumstances (e.g., late-stage diagnosis due to inadequate access to healthcare), there are emerging data that indicate that genetics and biology also play a role. Polygenic scores confer risks that vary by Self-identified Race and Ethnicity (SIRE); genetic ancestry is correlated with cancer risk or outcomes independently of SIRE; and tumour phenotypes and mutational signatures differ by SIRE. Because the relative contributions of genetic, biological, and social drivers of cancer aetiology remain unclear, approaches aimed at reducing inequities remain inadequate.

BARRIERS AND OPPORTUNITIES

Research to address cancer inequities has suffered from a number of limitations:

Firstly, prior approaches have been siloed within disciplines and have not leveraged data addressing the multifactorial contributions of genetics, biology, demographics, social drivers and circumstances, contextual factors, and health care delivery.

Secondly, the definition of groups being compared in studies of cancer inequities have been largely based on SIRE. Thoughtful consideration of the groups of interest, including definitions based on genetic ancestry or multivariate features that include social position or circumstances, may be required.

Finally, most of the work that has informed our understanding of cancer aetiology has been undertaken in European ancestry populations. New modalities and technologies for prevention, early detection, screening, and treatment have largely not been developed or tested in diverse populations. As a result, these previous modalities and technologies may have created or exacerbated health inequities.

To optimise the generalisability and impact of approaches addressing inequities, this challenge requires diverse data and data collection infrastructures, transdisciplinary methods to address the complex, multifactorial nature of cancer inequities.

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

- What is the relative contribution of genetics, biology, social determinants, and individual-level risk factors on inequities or disparities in cancer risk and outcome?
- Do genetic factors modify the effect of social inequities in determining cancer risk and outcomes?
- Among self-identified race and ethnicity, genetic ancestry, multifactor/multilevel indices, or other novel metrics of group membership, what is the optimal measure to assess differences, inequities, or disparities in cancer risk or outcome?
- Can combinations of genetics, genomics, exposures, risk factors, demographics, biological markers, tumour markers, tumour phenotypes, or other variables be used to define population subgroups that will optimally benefit from interventions that reduce inequities or disparities in cancer outcomes?

Teams may choose to develop and evaluate novel metrics for social determinants that can be translated into intervention and go beyond descriptive analyses.

VISION AND IMPACT

This challenge seeks to generate functional and mechanistic insights into cancer inequities by generating new transdisciplinary approaches applied in diverse populations.

An interdisciplinary team that represents diverse sectors, including genetics, biology, social and population science, health care delivery, health economics, diagnostics, biostatistics, bioinformatics, artificial intelligence, and others will be required to address this challenge. Applicants are strongly encouraged to establish global collaborations to generate knowledge that will be applicable worldwide.

This challenge will lay the groundwork for the development, evaluation, and implementation of future prevention, early detection, and treatment strategies to achieve equity in cancer outcomes for all people.

Understand and prevent chemotherapy-induced neurotoxicity and neuropathy

CONTEXT

Many patients suffering from cancer receiving cytotoxic chemotherapeutic agents such as platins and taxanes develop neurological toxicities such as peripheral neuropathy and ototoxicity, which can severely impact their day-to-day functioning and health-related quality of life. The effects on the central nervous system of chemotherapy can also lead to neurocognitive deficits in some patients with long-lasting consequences. This is commonly found after breast cancer treatment, for example. Despite this, there is limited understanding of why this occurs.

Understanding the biological mechanisms of these toxicities would provide insights into the impact of cancer therapies on neurobiology, enable the identification of biomarkers to predict patients at risk, propose strategies to prevent their occurrence, and offer therapeutic solutions to alleviate these debilitating side effects of chemotherapy.

BARRIERS AND OPPORTUNITIES

Chemotherapy remains a mainstay in the treatment of many cancers. Chemotherapy-induced neurological toxicity severely impacts patients' quality of life and may affect cancer outcomes by limiting clinicians' ability to deliver adequate treatment.

Pre-clinical models and clinical studies have not led to any reliable way to predict those who are most susceptible to these adverse effects. Currently available preventative measures and treatment remedies have limited effectiveness and are not uniformly applied in the clinic.

This challenge calls for bold and novel approaches to gain understanding that could help to prevent and treat chemotherapy-induced neurotoxicities, including but not limited to:

- Establishing a comprehensive hormonal, molecular and immunological understanding of mechanisms underlying the occurrence of chemotherapy-induced neurotoxicities
- Developing reliable preclinical models to recapitulate these conditions
- Applying knowledge from other disciplines e.g., neurobiology to increase our understanding of the mechanisms of these toxicities

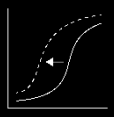
- Developing valid predictive biomarkers to identify patients at highest risk of peripheral neuropathy, ototoxicity and neurocognitive effects
- Proposing innovative measures to prevent and treat chemotherapy-induced neurotoxicities

VISION AND IMPACT

This challenge will bring together a concerted effort to maximise our understanding in the pathophysiology of chemotherapy-induced neurological toxicities.

This will require an inter-disciplinary research team involving clinicians, molecular biologists, neurobiologists, biochemists, immunologists, and patient survivors.

The knowledge gained from this challenge will enable the development of hypothesis-driven clinical trials in the prevention and treatment of chemotherapy-induced neurological toxicity, rendering these side effects no longer dose-limiting in the treatment of cancer patients.



Determine why the incidence of early-onset cancers in adults is rising globally

CONTEXT

Since the mid-20th century the incidence of early-onset cancers, defined as cancers diagnosed in adults under 50 years of age, has been rising globally.

In this demographic, cancers in the bone marrow, breast, colorectum, endometrium, extrahepatic bile duct, gallbladder, head and neck, kidney, liver, oesophagus, pancreas, prostate, stomach, and thyroid have increased globally. Some of this may be attributed to the increased implementation of screening programmes, but this does not explain the full picture.

Changes in the exposome and the environment in recent generations may in part explain this observation, including changes in diet, the microbiome, physical activity, obesity, alcohol consumption, sleep patterns, antibiotics use, stress levels, pollution, or environmental contaminants among others.

Understanding and preventing the increase in the incidence of early-onset cancers is now critical to address this emerging global health problem.

BARRIERS AND OPPORTUNITIES

To address the emerging issue of early-onset cancers, we need to understand the mechanisms linking lifetime exposures in multiple cancer types with cancer initiation and promotion.

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

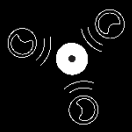
- Can we elucidate the mechanisms linking exposure types to cancer initiation and promotion, to explain the lack of an obvious mutational burden on many of the patients with early-onset cancer?
- Will the use of data and samples from existing prospective cohorts enable us to understand the impact of environmental insults, particularly early in life?
- Can we gain a better understanding of early-onset cancers from a genetic, genomic, epigenomic, transcriptomic and immunologic point of view?

To address this challenge, proposals could include pilot interventional studies on how to implement risk stratification and risk reducing interventions in younger populations.

VISION AND IMPACT

The goal of this challenge is to gain a robust understanding of the mechanisms underpinning the biological and environmental causes behind the global phenomenon of early-onset cancers. Addressing this challenge will require an inter-disciplinary team that could include epidemiologists, biologists, environmental scientists, geneticists, and optimally could involve oncologists from high-, middle-, and low-income countries.

If we better understand the mechanisms by which changes in the exposome lead to higher cancer burden at a younger age, translatable interventions that may reduce the associated morbidity and mortality may be designed subsequently. Please note that the development and testing of interventions are not required in proposals.



Determine the mechanisms through which obesity and physical activity influence cancer risk

CONTEXT

Obesity and sedentary behaviour are important risk factors for cancer. With over 4 billion adults and nearly 3 million children being overweight or obese, this is a significant global health concern. Previous studies and large meta-analyses have provided convincing evidence that obesity is associated with an increased risk of 13 cancers, and physical activity is associated with reduced risk for 6 different cancer sites. Yet, despite decades of research, the causative mechanisms linking obesity to cancer development and progression are not understood.

The challenge is timely due to recent advances in measurement, data science and emerging artificial intelligence (AI) methodologies, the availability of effective new drugs to treat obesity, experimental policy interventions around the world and new tools from basic science. Together, these provide the foundation for a new era of discovery research to understand the mechanistic links between obesity and cancer that could be translated into effective interventions.

BARRIERS AND OPPORTUNITIES

Much is known about the impact of obesity and physical activity on cancer, but the causative biological mechanisms are not understood. This has hindered the development of effective interventions.

Recent advances in high-throughput assays to measure biological features, e.g., the genome, methylome, metabolome, transcriptome, microbiome, and proteome, together with the creation of large research consortia and population biobanks, have vastly expanded the availability of high-dimensional molecular datasets from human samples, many of which are accessible through a range of bioinformatic platforms.

This challenge aims to go beyond collection of “omics” datasets, to seek a mechanistic understanding of the processes underlying cancer risk, causation and progression mediated by obesity.

The challenge seeks to answer questions such as, but not limited to:

- How do obesity and physical activity influence cancer at the molecular level?
- Does weight loss impact or can it reverse cancer risk, if so, what is the biological mechanism(s) involved?
- Does age of weight gain/loss affect risk and if so, what are the mechanisms?

- Does fitness reduce cancer risk among those with higher BMIs and, if so, how?
- How do new anti-obesity medications and gastric banding influence cancer risk?
- What is the dose-response relationship between physical activity and cancer?
- What can be done to reduce inequities in risk factors?

VISION AND IMPACT

This challenge seeks to build on the observed association between obesity and sedentary behaviour and cancer risk and to understand causative mechanisms to inform interventions to alter risk.

New measurement tools and methods, including improved biomarkers of risk, are needed. Success will likely require collaborations among basic, clinical, population scientists and others (e.g., engineers, policy experts). Animal models, data science, AI and other tools could advance discovery and help to identify interventions that can be translated into humans. The challenge is not aimed at testing alternative weight loss diets. Pilot tests of interventions could be derived from discoveries about mechanisms.

Understanding the effects of obesity and physical activity on cancer will accelerate development of interventions to reduce global cancer incidence and mortality and prolong survival. This will have population impact worldwide.

Understand the roles of retrotransposable elements in cancer

CONTEXT

It is now 80 years since Barbara McClintock discovered mobile genetic elements in Maize. Since that discovery the existence and mobilisation of such elements in humans has been broadly established. These elements are both widely dispersed and deeply embedded in our genome. Repressive mechanisms operate to supress their activation, and conversely, they are co-opted by the host to act as gene regulators. Therefore, retrotransposable elements contribute broadly to normal cell function.

Increasing evidence suggests that retrotransposable elements play a role in the initiation and progression of certain types of cancer, but the specific mechanisms are not well understood. Tools now exist to explore the extent of retroelement activation, how cancer cells respond to it, the consequences of genetic instability that retroelement propagation and dispersal causes in cancers as well as how this might contribute to cancer evolution.

Advancing the study of retrotransposable elements would allow a greater understanding of therapeutic vulnerabilities in cancer.

BARRIERS AND OPPORTUNITIES

Little is known about the genomic organisation or mechanisms that drive retrotransposable element reactivation or reintegration in cancer that could be targetable. Furthermore, current short read sequencing platforms and computational tools have rendered the study of retrotransposable elements challenging.

However, newly developed techniques, linked with interdisciplinary approaches, such as combining expertise in genetics, cancer biology, immunology, and bioinformatics will shed further light in understanding the role of retrotransposable elements in cancer to potentially uncover therapeutic vulnerabilities in cancer.

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

- Can we quantify the extent of retro transposition in cancer cells in vivo and in vitro?
- To what extent are retrotransposable elements activated in cancers?
- Do cancers suppress pathways that silence these elements? If so, how, and why?

- To what extent do retrotransposable elements fuel insertional and also gross chromosome mutagenesis?
- Do cancer cells co-opt retrotransposable elements as regulatory DNA sequences to favour cell division?
- How do they influence intracellular immune responses?
- To what extent do retroelements give rise to endogenous retroviruses and shape the tumour microenvironment, and more generally host responses?
- Could derepressing retrotransposition or inhibiting DNA repair of the invading elements provide therapeutic opportunities in treating cancer.

VISION AND IMPACT

Addressing this challenge will solidify our understanding of how retrotransposable elements are regulated, evolve, reactivate, and reintegrate. This could provide new therapeutic targets to maintain genome stability in cancer, prevent retroelement reactivation, and understand their impact on the innate immune system.

An interdisciplinary team will be required to address this challenge, which could coalesce the fields of cellular and evolutionary biology, cancer genomics, DNA repair, bioinformatics, and immunology, among others.

Develop therapeutics to target oncogenic drivers of solid tumours in children

CONTEXT

Cancer remains the leading cause of death by disease in children globally, and progress in the treatment of children with solid tumours (which includes brain tumours) has largely 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 most paediatric solid tumours, standard curative treatment regimens continue to rely on cytotoxic agents, developed decades ago, and often radiotherapy. Such therapies induce an alarming rate of severe late effects, including second malignancies, cardiac, neurologic, and skeletal toxicity, and infertility. Targeted therapeutics are needed to improve outcomes for paediatric cancers.

BARRIERS AND OPPORTUNITIES

Tumours arising in children differ from those occurring in adults. Whereas mutant kinases commonly drive adult cancers and kinase inhibitors have had great impact in the treatment of adult cancers, oncogenic drivers in children's solid tumours are typically transcription factors and/or epigenetic proteins which have historically been considered "undruggable". Compounding the biological challenges, drug development in biopharma for paediatric solid tumours has not been prioritised, due to the small market size.

New platforms show promise for targeting transcription factors and epigenetic pathways, including selective protein degraders, molecules that disrupt essential protein-protein interactions and cell selective delivery of oligonucleotides to modulate gene expression.

Questions that could be addressed in this challenge include, but are not limited to:

- Can we develop protein degraders that selectively target oncogenes that drive paediatric cancers, and do they regress tumours in preclinical models? Does E3 ligase biology vary between adult's and children's solid tumours?
- What are the major resistance pathways for protein degraders in paediatric cancers? What type of protein degrader is most suited for this setting (e.g., molecular glues vs. heterobifunctional degraders) and what targets are susceptible to this approach?

- How do degraders compare to emerging small molecules that work by disrupting protein-protein interactions or oligonucleotides? Can we use midsize cyclic proteins to target undruggable targets?
- Can we identify targeted therapeutics that should be prioritised for clinical testing in paediatric solid tumours?
- What is the toxicity profile of these agents in children?

VISION AND IMPACT

Paediatric cancer drug development is inefficient and resources to develop drugs for paediatric cancers are often rate limiting.

An interdisciplinary and disruptive team capable of discovering, developing, and conducting early clinical testing of novel targeted therapeutic(s) is needed. Members could include cancer biologists, developmental biologists, clinical investigators, animal modellers, and medicinal chemists. Applicants should include a rationale for the age range of the participants in any proposed studies and how this would address the challenge.

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

Decipher the T-cell receptor cancer-recognition code

CONTEXT

Many cancers harbour tumour-infiltrating T cells that are potentially reactive to cancer (neo)antigens. While it is possible to sequence the T-cell receptors (TCR) present on these immune cells, it is presently not possible to use this information to comprehensively and at scale infer the antigen that is recognised by the receptor. Deciphering the T-cell receptor code will allow accurate prediction of the nature of the cancer antigens that T cells detect based on their T-cell receptor sequence. A better understanding of the interaction between the major histocompatibility complex (MHC)-bound antigens and the T-cell receptors has the potential to greatly improve future cancer immunotherapies as well as understanding and treatment of autoimmune and infectious diseases.

BARRIERS AND OPPORTUNITIES

The recent success of Tumour Infiltrating Lymphocyte (TIL) cell therapy highlights the notion that TILs can be tumour-reactive. Unfortunately, in most cases the nature of the antigens recognised by the TCR present on these TILs is unknown. Knowledge of the antigens that are recognised by TILs will provide opportunities to potentiate the immune responses against cancer cells and to develop advanced cellular therapies.

Overcoming this barrier calls for new approaches to predict the nature of the antigen(s) recognised by TIL TCRs.

Such approaches could include, but are not limited to:

- High throughput identification of TCR-sequences/ antigen complexes and prediction/ elucidation of their structures and specificity
- Development and use of AI and/ or machine learning tools to identify relationships between TCR sequence and antigen structure
- Development and validation of a tool to predict the (neo)antigens recognised based on a TCR sequence

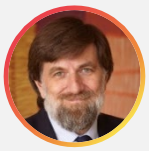
VISION AND IMPACT

This challenge seeks to develop a comprehensive understanding of the TCR-peptide-MHC interaction and to improve our knowledge of the nature of the cancer antigens that are recognised by T cells. Addressing

this challenge will require an inter-disciplinary team that could include structural biologists, immunologists, computational biologists with knowledge of artificial intelligence/ machine learning tools and high throughput screening specialists.

The ultimate goal of this challenge is to improve and broaden the efficacy of cancer immunotherapies and therefore proposals could include initial (pre-clinical) proof-of-concept studies to validate the tools developed by the challenge team.

Appendix 2: Scientific Committee membership

	Professor Sir **David Lane** Chairman (UK)
	Professor **René Bernards** Netherlands Cancer Institute (Netherlands)
	Professor **Judy Garber** Dana-Farber / Harvard Cancer Center (US)
	**Margaret Grayson** MBE Chair, Cancer Grand Challenges Advocacy Panel (UK)
	Professor **Michael Hall** University of Basel (Switzerland)
	Professor **David Hunter** University of Oxford (UK)
	Professor **Sherene Loi** Peter MacCallum Cancer Centre (Australia)
	Professor **Crystal Mackall** Stanford University (US)
	Professor **Jill Mesirov** University of California San Diego (US)
	Professor **Ketan (KJ) Patel** University of Oxford (UK)
	Professor **Timothy Rebbeck** Harvard TH Chan School of Public Health / Dana-Farber Cancer Institute (US)

	Professor **Barbara Rimer** University of North Carolina (US)
	Professor **Lillian Siu** Princess Margaret Cancer Centre / University of Toronto (Canada)
	Professor **Charles Swanton** The Francis Crick Institute / University College London (UK)
	Professor **Karen Vousden** CBE The Francis Crick Institute (UK)

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