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.

Contents

1. Summary of key dates

1. Complete questionnaire	2. Submit EOI	3. Shortlisting	4. Submit full application	5. Award starts
11 June 2025	18 June 2025	July 2025	23 October 2025	2026

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 grants 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 assemble their team 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 02-04 December 2025. The CGCSC will recommend which teams should be funded.

5. Award

Winning team members will enter into a Cancer Grand Challenges Award Agreement and begin their research in May 2026.

2. About Cancer Grand Challenges

Team science on a global scale

Cancer Grand Challenges supports a global community of world-class, interdisciplinary research teams to come together, think differently and take on some of cancer's toughest challenges, with the ultimate aim of transforming outcomes for people affected by cancer.

Founded by two of the largest funders of cancer research in the world – Cancer Research UK and the National Cancer Institute in the US – Cancer Grand Challenges has the power to create change. The initiative is also supported by Cancer Research UK's global network of partners and philanthropists who share our ambitions.

By galvanising the international scientific community and giving researchers the freedom to innovate, we are accelerating the discoveries that are needed to make substantial progress against cancer.

*Cumulative figures.

Cancer's toughest challenges

Cancer Grand Challenges leads a global debate with the research community and people affected by cancer to identify cancer's most complex challenges, and then dares global, interdisciplinary research teams to apply to take them on. The Cancer Grand Challenges community has now taken on 13 cancer grand challenges to date. We've now announced seven ambitious new challenges – see Appendix 1.

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 (e.g. investigator-initiated research grants).

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 scientifically 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 scientifically 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 include investigators, who are based in the UK or US or any other specific country.

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; computational sciences and technology; engineering and physical sciences; and behavioural, health, population and social sciences.

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 required to recruit a part-time programme manager (see section 4.5) at full application stage; and then a full-time programme manager if funded.

Researchers may participate in only one application per funding call. Patient advocates may participate in only one application per funding call, and advocates already embedded in a funded team may not participate in new applications.

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. Proposals to include multiple Team Leads will not be considered.

The 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.

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.

Teams may include up to seven Co-Is. It is expected that all Co-Is will receive significant funding in order for them to make a substantial contribution to a team. Co-Is must contribute at least 10% of their research time to the Cancer Grand Challenges award. Proposals to include more than seven Co-Is will not be considered.

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.

At the EOI stage, you should broadly describe how you will involve people affected by cancer in your scientific programme, and how you will engage the public with your research. 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 their respective TL and Co-Is to develop detailed involvement and engagement plans for their teams. They will then be critical in delivering and implementing these plans.

4.5. Programme manager

Shortlisted teams are required to recruit a part-time programme manager (PM) to assist the TL and Co-Is in meeting the requirements of the full application. If funded, teams must hire a full-time PM to assist the TL and Co-Is in coordinating activities of the research consortium. The PM's responsibilities could include, but aren't limited to:

- Assisting the CGC TL and Co-Is in monitoring and ensuring team compliance with 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;
- Manage roster of participating future leaders across the team;
- 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

The Terms and Conditions of Cancer Grand Challenges funding, and policies affecting awards, are set out in a series of documents, updated versions of which will be shared with shortlisted teams.

The documents that have been issued to existing funded teams are available on our website, and it is anticipated that the updated versions will resemble them. Teams are therefore asked to familiarise themselves with these documents at the earliest possible juncture, and to disseminate them to their fellow researchers and host institutions. The Terms and Conditions of Cancer Grand Challenges funding are not negotiable. Shortlisted teams will be required to confirm that every participating institution is able to adhere to the Terms and Conditions and to sign the Cancer Grand Challenges Award Agreement. Any team unable to do so will not be considered for funding.

The relevant documents are:

- **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.

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.

It is necessary for Cancer Research UK to share personal data from any application with certain funding agencies in the United States. 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 certain funding agencies in the United States.

You may withdraw consent for your data to be shared with certain funding agencies in the United States 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 incurred in accepting the funding (those costs that arise from the conduct of the research undertaken and are verifiable from accounting records). No more than 70% of a team's funding may be issued to institutions in a single country.

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

Shortlisted teams will be asked to provide a full budget for direct costs, and will be advised of any indirect costs to be awarded if funded. The funding model and indirect cost rates for existing Cancer Grand Challenges teams are available for reference on our website.

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 specific individual for 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 11 June 2025, 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 18 June 2025.

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.

The EOI template may not exceed three pages, not including the financial overview.

Section of EOI template	What it should cover
Team	List of team members
Summary	Overview of your team's approach to solving the challenge • Description of the proposed research • Rationale for team make-up
Outputs and impact	Expected outputs and impact of your proposal
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).
Financial overview	Predicted direct costs 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

Using generative Artificial Intelligence tools when building your full application

You are advised to use caution in relation to the use of generative Artificial Intelligence (AI) in developing your application and to stay up to date with relevant policies and guidance. Applicant teams must:

- Support the highest levels of research integrity as set out in section 3.2.4 of the Award Management and Policy Guide.
- Ensure generative AI tools are used in accordance with relevant legal and ethical standards, including data privacy where those standards exist or as they develop.
- Use generative AI tools responsibly to ensure the originality, validity, reliability and integrity of outputs created or modified by generative AI tools. This includes ensuring applications contain accurate information and do not contain false or misleading information.
- Correctly and explicitly attribute outputs from generative AI tools in applications by listing the generative AI source, where practicable, naming the specific model/s used and software, and specifying how content was generated (such as listing the prompt used).
- Adhere to host institution policies on the use of generative AI tools, particularly those concerning plagiarism and fabrication.

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 may not exceed one side of A4.

Section	Detail
Academic details	• Name, position, institution, location • ORCID number if applicable • Professional qualifications • Positions and accolades
General	• What are your five greatest contributions to research? • List publications related to these research contributions and note any relevance to the CGC application. You may also link to a MyBibliography, ResearchGate, or similar site.
Other support	• Current funding >£1m (lifetime value) and % level of effort allocated to each

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.

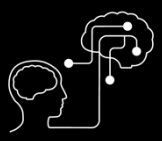
8. Contact details

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



Develop interdisciplinary AI agents that can generate novel cancer research hypotheses and design research plans for them to be experimentally validated

CONTEXT

Cancer research continues to become more complex. Research questions increasingly require a wide range of expertise to address. Additionally, there is a growing volume and variety of data that spans scales from molecular data to epidemiological data. Furthermore, publications are increasing at an exponential rate making it more challenging to identify the most important new findings. However, recent advances in AI can help overcome these challenges. Large language models (LLMs) have been trained on vast quantities of text data, including scientific literature, and have shown high accuracy in answering scientific questions. Early work has begun to explore the use of LLMs to conduct scientific research.

This challenge aims to go beyond the ability of AI to extract information, make predictions, or conduct standard research tasks, making the leap to AI agents that can collaborate with humans to generate paradigm-shifting discoveries that advance cancer research. Agents are layers on top of LLMs that observe and collect information, provide input to the model, can conduct complex tasks, can have specific expertise, and can work together with other agents and humans.

BARRIERS AND OPPORTUNITIES

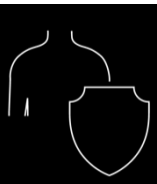
This challenge will require technological innovation to develop AI agents that can generate novel hypotheses that address important challenges in cancer research. The AI agents will also need to develop research plans to test these hypotheses that can be experimentally validated. Iterative cycles of experimental design and validation may be required. It is likely that multiple AI agents with different expertise and purposes will be required. It will also be important for there to be a human-in-the-loop to provide high level guidance and context that AI agents may lack.

The cancer research question that the AI agents are addressing should be complex and transdisciplinary and go beyond straightforward tasks and predictions. Of particular interest is cancer initiation and progression and the development of AI agents that can investigate the malignant conversion of precancerous lesions across tissues and identify novel therapeutics to prevent cancer initiation or progression in patients at risk.

This challenge will require close collaboration between AI researchers and cancer researchers and may also include machine learning specialists, data scientists, biologists, clinical researchers, and ethical advisors. Strategic academic-private partnerships are encouraged, with private partners contributing funds.

VISION AND IMPACT

This challenge seeks to transform cancer research by advancing AI-driven tools and methods. It will enable the integration of the rapidly growing volume of cancer data and knowledge into AI-generated hypotheses. By fostering human-AI collaboration, this challenge aims to tackle complex cancer research questions, with the potential to reshape our understanding of the disease and identify new therapies.



Understand the mechanisms by which certain high-risk populations or the extremely aged are resistant to developing cancer

CONTEXT

Cancer research has traditionally focused on identifying drivers of cancer rather than barriers to its development. Intriguingly, there are sub-sets of individuals with well-established cancer risks who, despite this predisposition, never develop cancer. For example, over 20% of patients with BRCA1 germline mutations, will not get cancer and only 10-20% of heavy smokers will suffer from lung cancer, in their lifetimes. Furthermore, although cancer risk generally increases with age, paradoxically, after age 80-85, the incidence of many cancers starts to plateau or even decline.

Similarly, certain human progeria syndromes, such as Hutchinson-Gilford, appear resistant to cancer despite significant cellular stress. Additionally, some larger long-lived mammals exhibit unexpectedly low cancer incidence, a phenomenon known as Peto's paradox.

Several biological and epidemiological explanations have been proposed to explain these observations. However, the mechanistic basis underlying these phenomena remain unexplained.

This challenge seeks to uncover the biological mechanisms underpinning tumour resilience in the host to understand what protects certain individuals from developing cancer.

BARRIERS AND OPPORTUNITIES

Mechanisms that prevent cancer initiation and development are likely diverse, involving a complex interplay of molecular, cellular, and systemic factors such as immune surveillance, inflammation, lifestyle and environmental exposures, including diet. Individuals may also possess rare protective mechanisms against tumour initiation, making them difficult to detect.

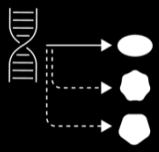
A major challenge in understanding cancer evasion is the scarcity of longitudinal data on high-risk individuals who remain cancer-free. Additional complexities include the influence of risk-reducing strategies and selection bias, known as the 'Survivor Effect'.

Addressing this challenge may require a systems-wide approach, utilising adequately powered and phenotypically rich cohorts and integrating fields such as, but not limited to genomics, ageing, immunology, metabolism, epidemiology, comparative zoology and artificial intelligence.

VISION AND IMPACT

This challenge will identify the underlying mechanisms as to why some individuals manage to avoid cancer, despite predisposition, due to genetic or lifestyle risk factors or extreme old age.

These findings could change our understanding of cancer development, inform novel therapeutic approaches and ultimately help devise cancer prevention strategies for the general population.



Understand and exploit the dark proteome for cancer therapy

CONTEXT

Recent data indicate that cancer cells express proteins that are not derived from known open reading frames as well as proteins with alterations in amino acid sequences without corresponding DNA mutations. The origins of this 'dark proteome' remain elusive.

This challenge aims to define the mechanisms underlying the induction of these dark proteome products and understand their relationship with the oncogenic state of the cancer cell. It is also an opportunity to use them as therapeutic targets and understand whether the dark proteome is a source of non-mutated tumour-selective antigens and synthetic lethalities and determine whether these products can be targeted by immunologic or small molecule-based therapies that could be adapted to become 'off the shelf' treatments.

The focus of the challenge is on understanding the mechanisms giving rise to non-standard protein products (the dark proteome) and their impact on cancer.

BARRIERS AND OPPORTUNITIES

Current examples of the dark proteome (including many so called microproteins) may be the tip of the iceberg. More work is needed to understand how these proteins are generated and to elucidate the role that they play in oncogenesis. A key question could be whether these products give rise to non-mutated antigens and whether they are universally expressed between individuals and across tumour types. Dark proteome products may be immunogenic, but it is unclear if they undergo the same immuno-editing as conventional antigens.

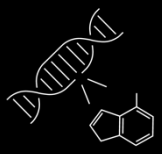
Similarly, understanding how the dark proteome functions in tumours could then be applied to the selective disadvantage of the tumour cell or to the advantage of the immune system.

Addressing this challenge may require integrating fields such as but not limited to immunology, cell biology, genetics, RNA and protein biology, mass spectrometry, synthetic and analytical chemistry as well as oncology.

Note: Applications that focus on non-coding RNAs, RNA editing/ mutations and retroelements that do not produce a protein product as well as applications that focus on alterations in RNA splicing will not be considered responsive to this challenge.

VISION AND IMPACT

This challenge will reveal the fundamental molecular mechanisms leading to the expression and regulation of the dark proteome and determine their role in cancer versus normal cells. Based on this understanding, strategies to manipulate the expression of these unconventional protein products could be developed. Defining how this process is perturbed in cancer cells may uncover new opportunities to target tumours with immunologic or small molecule-based therapies, exploiting this selective vulnerability in cancer.



Identify the insults responsible for unexplained mutational signatures

CONTEXT

Exposure to carcinogens can elicit specific patterns of DNA damage (mutational signatures). The recent surge in whole-genome sequencing of normal and cancerous tissues has led to the identification of an increasing number of these signatures.

To date, there have been at least 86 distinct single-base pair and dinucleotide mutational signatures identified but the aetiology of many of these remains unknown. Some of these mutations likely result from error-prone translesion DNA synthesis over chemically altered bases, known as DNA base adducts. However, a significant gap remains in our understanding of the exact nature of these adducts, how they arise and how they contribute to mutation formation. Without addressing this fundamental gap, we cannot fully explain the origins of many mutational signatures or develop strategies to prevent them. Identifying these base adducts could reveal whether they arise from endogenous processes or exogenous sources and aid identification of the mutagens responsible and inform public health measures.

This challenge would allow the identification of the mechanisms that lead from insult to mutation, and ultimately, realise the potential of mutational signatures to inform cancer prevention.

BARRIERS AND OPPORTUNITIES

This challenge will require technological innovation to resolve the chemical composition of normal versus damaged DNA in an unbiased manner, expanding the identification of altered DNA bases beyond what is currently possible (overcoming limitations of abundance, co-occurrence and stability of adducts).

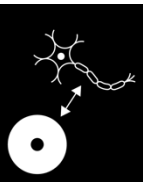
The discovery of novel exogenous and endogenous mutagens may prompt the development of a reimagined AMES test linking the mutagen to the base adduct and the genesis of a point mutation.

Addressing this challenge may require the collaboration of organic, synthetic and analytical chemists, state-of-the-art nucleic acid and small molecule mass spectrometry, and single molecule sequencing method development, as well as biologists with expertise in mutagenesis and DNA repair through to epidemiologists.

VISION AND IMPACT

This challenge will result in the ability to analyse the base composition of the genome in an unbiased manner, ushering in a new age of discovery for DNA base modifications.

Identifying the chemistry that initiates mutational signatures, will advance understanding of the mechanisms of cancer initiation and may allow new public health measures in cancer prevention to reduce cancer risk.



Understand the dynamic interactions between the nervous system and cancer

CONTEXT

Nerves mediate the homeostasis of normal tissues, and this is disrupted in neoplasia where the nervous system promotes cancer pathogenesis, therapeutic resistance, pain syndromes and psychological dysfunction. In response to signals released by tumours, peripheral nerves arborize and bidirectionally communicate with them to promote cancer progression and immune dysfunction. Beyond cancer, evidence suggests that Parkinson's disease may initiate in the gut and impact the brain via the vagus nerve. Despite these insights, the underlying molecular mechanisms remain poorly defined.

This challenge aims to define bidirectional signalling between tumours and the peripheral and central nervous systems that promote cancer progression. These findings will yield new biological mechanisms that could underpin therapeutic intervention and improve patient outcomes.

BARRIERS AND OPPORTUNITIES

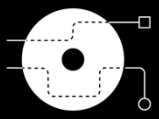
The role of nerves in cancer biology remains poorly understood, presenting an opportunity to bridge oncology and neuroscience. Neuronal contributions to cancer may be underestimated due to the difficulty of detecting nerves within tumour tissue. Addressing this challenge will require innovative approaches to investigate nerve-tumour interactions with precision.

This challenge will explore whether nerves actively drive cancer pathogenesis, influence immune recognition or the systemic effects of cancer and therapeutic response. This could include the potential role of nerves as sanctuary sites for neoplastic cells or pathways for metastatic spread. Investigating how nerves mediate these cancer-associated factors could provide crucial mechanistic insights.

Applications are strongly encouraged from teams which bring together expertise in neuroscience with cancer biology and immunology to explore interactions between the nervous system and a broad range of tumours across the body, beyond neural tumours or those confined to the nervous system.

VISION AND IMPACT

Identifying and developing a mechanistic understanding of the bidirectional communication between tumours and the nervous system will ultimately reveal new fundamental insights about cancer progression, that could be developed into novel approaches for the treatment of cancer.



Develop and apply novel ways to rewire cancer cells to their disadvantage

CONTEXT

Inhibition of oncogenic signalling in advanced cancers often results in secondary mutations that restore oncogenic signalling in the presence of drugs, indicating that we must consider fundamentally different approaches to treat cancer.

Insights gained over the past two decades have yielded a detailed knowledge of how cells are wired and how proliferation and survival signals are altered in cancer cells. Moreover, advances in synthetic biology, such as proximity-inducing molecules allows proteins that normally would not interact to come together, providing opportunities to change the wiring inside a cancer cell from a signal that promotes oncogenesis to one that has an opposite effect on cancer cells. Emerging approaches to overstimulate oncogenic signalling beyond a cell's 'goldilocks' level, also provide opportunities to steer cells to less malignant phenotypes, as cancer cells may escape the drug-induced overactivation of oncogenic signalling through suppression of intrinsic oncogenic signalling.

This challenge aims to develop inventive ways to rewire cancer cells to a less malignant phenotype as a novel approach to therapy.

BARRIERS AND OPPORTUNITIES

Addressing this challenge will require methods to determine which cancers or cell types would be susceptible to a particular rewiring approach, and whether further cancer types can be made susceptible using innovative approaches.

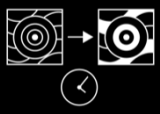
Novel ways to target heterogenous tumour cell populations should also be considered, for instance affecting non-responsive cancer cells in a heterogeneous population, by making responding cells more immunogenic, by means of executing an immunogenic form of cell death or by driving cell populations into a more uniform state.

Note that applications should not focus on targeted protein degradation approaches.

An interdisciplinary team will be required, bringing together diverse areas of expertise, which could range from synthetic biology, artificial intelligence, medicinal chemistry and structure-based drug design to expertise in cancer biology, immunology and signalling.

VISION AND IMPACT

This challenge will develop novel and creative approaches to rewire cancer cells to a less malignant phenotype and provide proof of concept, fundamentally changing the way we think about cancer treatment. These innovative approaches could lead to an expanded arsenal of therapeutic strategies for cancer that overcome limitations associated with current treatment modalities.



Develop methods to identify the functional role of the tumour microenvironment over time

CONTEXT

Advances in spatial transcriptomics and proteomics have significantly advanced the characterisation of the cellular composition and heterogeneity of tumour lesions. Despite these advances, major gaps remain in understanding the functional interactions that drive organisation and the formation of microanatomical niches of the tumour microenvironment (TME), how the TME evolves over time and during exposure to therapies, and how specific TME organisation promotes tumour growth or resistance to current therapies.

Standard biopsy and histology approaches provide static snapshots, failing to capture the diverse but spatially restricted and evolving cell populations that may drive therapeutic resistance. Moreover, the TME continuously evolves, responding to tumour cues, cellular interactions, immune pressures, metabolic changes and therapeutic interventions.

This challenge goes beyond mapping the TME and aims to develop new methods to interrogate over time and at a functional level, interactions between the cellular, stromal, and non-cellular components of the TME to understand cancer development, progression and response to therapy.

BARRIERS AND OPPORTUNITIES

A major opportunity lies in obtaining longitudinal data on TME formation and evolution in patients, generating hypotheses that can be tested in preclinical models using dynamic functional spatial genomics and other approaches.

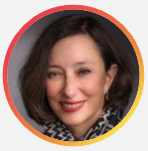
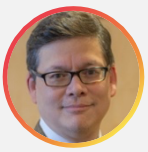
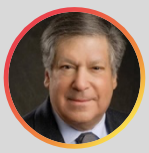
Interdisciplinary teams will be required to overcome barriers such as the need for novel sampling technologies that capture the full heterogeneity of the TME while preserving spatial integrity. Teams may also need to develop new tools to investigate functional inter-cellular interactions, incorporating AI and computational modelling to simulate and test hypotheses of which cellular interactions may drive cancer progression and therapeutic response or resistance.

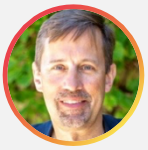
Note: applications focused on a subset of cell types in the TME, cross-sectional measurements of spatial organisation in the TME, studies only in animal models without guidance from human analyses, pure ‘mapping’ exercises, or studies lacking functional and longitudinal components will not be considered responsive to the challenge.

VISION AND IMPACT

This challenge will enable the dynamic functional profiling of the TME, elucidating the drivers of TME organisation and evolution, and the functional role of the TME in cancer development, progression and response to treatment. Understanding how these interactions dynamically shift over time and in response to therapy will inform next-generation treatment strategies that prevent resistance and enhance patient outcomes, ultimately reshaping cancer treatment and improving long-term survival.

Appendix 2: Scientific Committee membership

	Professor R. **Charles Swanton** FMedSci FRS (Chairman) The Francis Crick Institute / University College London (UK)
	Professor **Judy Garber** (Vice-chairwoman) Dana-Farber / Harvard Cancer Center (US)
	Professor **Fabrice André** Gustave Roussy (FR)
	Professor **René Bernards** ForMemRS MAE Netherlands Cancer Institute (NL)
	Professor **Benjamin Haibe-Kains** Princess Margaret Cancer Centre / University of Toronto (CA)
	Professor **Michael Hall** University of Basel (CH)
	Professor **Sherene Loi** Peter MacCallum Cancer Centre (AU)
	Professor **Miriam Merad** Icahn School of Medicine at Mount Sinai (US)
	Professor **Ketan (KJ) Patel** FMedSci FRS University of Oxford (UK)
	Professor **Timothy Rebbeck** Harvard TH Chan School of Public Health / Dana-Farber Cancer Institute (US)
	Professor **Robert Schreiber** Washington University in St. Louis (US)

	Professor **David Tuveson** Cold Spring Harbor Laboratory (US)
	Professor **Karen Vousden** CBE FMedSci FRS MAE The Francis Crick Institute (UK)

CANCER GRAND CHALLENGES

CancerGrandChallenges.org