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CANCER RESEARCH UK

Torrey Coast FOUNDATION | GEMINI

Application Guidelines:

Targeted Cancer Grand Challenges On Gastroesophageal Cancers

To discuss your application, please:

email info@cancergrandchallenges.org

phone +44 (0) 20 3469 8855

Contents

1. Summary of key dates and information

Submission deadline	Shortlisting outcome	Team interviews (in NYC)	Funding Decision
24 November 2026	Late-December 2026	20 January 2027	February 2027

1.1. Introduction

Recognising the urgent need for progress in gastroesophageal cancer research, the Torrey Coast Foundation and Cancer Research UK have partnered to launch a targeted Cancer Grand Challenges funding call on gastroesophageal cancers. The call seeks to fund international teams capable of bringing novel approaches, technologies and thinking to tackle two major challenges.

- **Challenge 1: Understand and reverse early tissue changes leading to gastroesophageal cancers**
- **Challenge 2: Determine the biological mechanisms underpinning geographical variations in gastroesophageal cancer incidence**

Note: This challenge excludes investigating the transition to, and from, Barrett's oesophagus, recognising the large number of spontaneous oesophageal adenocarcinomas that appear to arise in the absence of Barrett's. Please see **Section 9** for the full challenge articulations.

These guidelines explain the process for applying to the targeted Cancer Grand Challenges on gastroesophageal cancers, co-funded by the Torrey Coast Foundation and Cancer Research UK through Cancer Grand Challenges.

Please ensure that you and your research support office read these guidelines, alongside:

- The full challenge articulations; and
- The terms and conditions, and policies outlined in **Section 6.**

The deadline for submission is **24 November 2026** at **23:59 GMT**. Successful teams will receive up to **£25 million GBP** (direct costs). Please do not hesitate to contact the Cancer Grand Challenges office if you have any questions before you apply.

Applications are comprised of a publishable research abstract, research proposal (10 page limit), finance schedule, appendix (up to 10 pages), biosketch for the Team Lead and all Co-Investigators, schedule of Background Intellectual Property, letters of support from the host institutions of all team members, and letters of support from any collaborators or commercial partners (where applicable).

Please see **Section 8** for more information.

1.2. Application process

Applications will be reviewed by members of the Cancer Grand Challenges Scientific Committee (CGCSC) and other international experts with relevant expertise where required.

The review process consists of two stages:

1. **Application submission and shortlisting**: Applicants must first submit a confidential Letter of Interest (LOI) using the link provided on the funding call webpage. If an LOI is deemed eligible and within scope to the funding call by the Cancer Grand Challenges office, a FlexiGrant full application link will be provided to the lead applicant. The LOI is for administrative purposes only and is not subject to scientific assessment. Submitted applications will be assessed by the CGCSC against the published criteria, with selected applications being shortlisted and invited to interview.
2. **Interview and funding recommendation:** Shortlisted applications will be invited to interview in **New York City on 20 January 2027**. Applicants will receive reviewer comments in advance, having the opportunity to respond during the interview. Following the interview, the CGCSC will make funding recommendations to the Torrey Coast Foundation and Cancer Research UK, which will make the final funding decisions. All shortlisted applicants will receive feedback, regardless of the outcome.

1.3. Award

Teams will be funded by the Torrey Coast Foundation and Cancer Research UK through Cancer Grand Challenges. Winning team members will collectively enter into a Cancer Grand Challenges Award Agreement with one another and Cancer Research UK and will begin their research **1 May 2027**.

2. About Cancer Grand Challenges

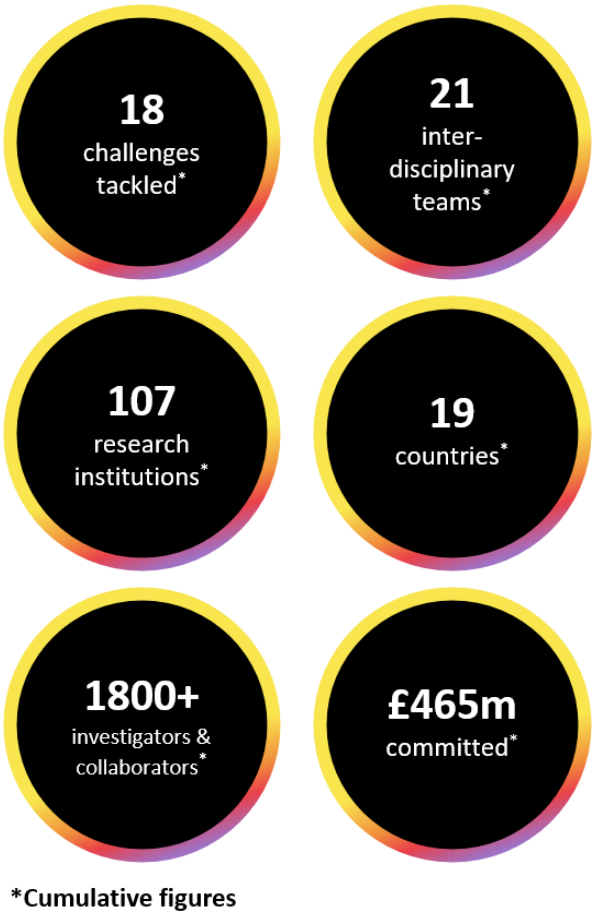
Team science on a global scale

Cancer Grand Challenges is a global research initiative that identifies the toughest challenges in cancer research. With awards of up to £25 million, it empowers a global community of world-class, interdisciplinary research teams to come together and take them on.

Founded in 2020 by the two largest funders of cancer research in the world – Cancer Research UK and the National Cancer Institute in the US – Cancer Grand Challenges has the power to create change and deliver the progress against cancer we urgently need.

The initiative is also supported by Cancer Research UK's global network of partners and philanthropists who share our ambitions. Please note that winning teams in this funding call will be funded by the Torrey Coast Foundation and Cancer Research UK through Cancer Grand Challenges.

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 18 Cancer Grand Challenges to date.

3. About the Torrey Coast Foundation

The Torrey Coast Foundation is a dedicated philanthropic organisation committed to accelerating breakthroughs in the treatment of gastroesophageal cancers. Through its funding and strategic support of the Gastroesophageal Malignancies Investigator Network Initiative (GEMINI), the Foundation fosters a collaborative ecosystem that unites leading scientists, oncologists, and research institutions to drive translational discovery from bench to bedside.

GEMINI, funded by Torrey Coast, catalyses innovative preclinical research and expedites the development of novel therapies by enabling rapid access to patient-derived tumour samples, advanced cancer organoid models, and genetically engineered mouse models. This network accelerates the translation of promising laboratory findings into Phase I clinical trials, empowering investigators to pursue high-risk, high-reward projects that traditional funding avenues may overlook.

By connecting multidisciplinary teams and supporting bold approaches to drug discovery and combination strategies, the Torrey Coast Foundation aims to expand therapeutic options and improve outcomes for patients affected by these aggressive cancers. Through targeted grant making and partnership-driven research, the Foundation plays a pivotal role in pushing the frontiers of gastroesophageal cancer science toward meaningful clinical impact.

4. What do we want to see from applicants?

Cancer Grand Challenges are intended to transform cancer research. Applications must reflect this ambition. We want to see bold proposals against the challenges we have set, and see evidence that applicants have actively sought out new, perhaps unusual, collaborations to bring fresh thinking from outside the field, 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 global, multi-disciplinary teams with the best ideas to address the challenges. We expect proposals to 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 include individuals with the potential to become future leaders in cancer research, as well as people affected by cancer to support patient advocacy.

The end point of a Cancer Grand Challenges award does not need to be a clinical intervention or impact within the duration of an award. However, Research Proposals should include a clear line of sight towards preventing, diagnosing or treating cancer as much as is possible. Applicants are encouraged to consider how transformative mechanistic discoveries could create opportunities for downstream translation and ultimately improve outcomes for people affected by cancer.

4.1. Assessment criteria

The CGCSC will review applications 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 articulated, in a way that fully takes advantage of the opportunity to pursue a large, coordinated, international team-based effort.
- **Innovation**: the work must involve the development of novel methodologies, approaches, theoretical concepts, instrumentation, resources and/or capabilities to tackle the challenge. 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 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; teams are encouraged to include researchers from outside the gastroesophageal cancer field.
- Be international, facilitating global collaboration between researchers; this includes researchers across countries with contrasting incidence, exposures and disease subtypes. Scientific leadership, governance, experimental work and analysis of samples and data should be shared across the team and between research centres. The challenge should not solely rely on the extraction of samples to a small number of established research centres.
- Incorporate training for future leaders (PhD students, Post Docs, and other early career researchers) in cancer research.

- **Impact**: The proposed research should have the potential to deliver significant long-term benefits for patients and/or the wider public. Applicants should articulate a credible pathway to translation where appropriate, recognising that meaningful improvements in cancer prevention, diagnosis and treatment are often enabled by transformative mechanistic discoveries.

5. Challenge teams

Teams must include only one Team Lead (see Section 5.1) and up to seven Co-Investigators (see Section 0). Funded teams will also be required to recruit a full-time **Programme Manager (see Section 5.54**).

Teams must be international, with no more than 50% of the activity (and funding) being based in a single country. There is no requirement for teams to comprise team members who are based in the UK or US.

Applications are welcomed and encouraged from teams working across a breadth of disciplines.

Applicants may only be listed on one application for this funding call.

CGCSC members are prohibited from applying in any capacity (i.e. a Team Lead, Co-Investigator, or collaborator); other researchers from their host institutions can apply.

5.1. Team Lead

Each team must have only one Team Lead. The Team Lead is responsible for the overall scientific and technical direction of the team. Proposals that include multiple Team Leads will not be considered.

The Team Lead will be expected to spend a significant proportion of their research time on the Cancer Grand Challenges award. Team Leads may only be listed on one application for this funding call.

The Team Lead 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.

Active CGC Team Leads are not typically eligible to apply as a Team Lead for another team but should contact their designated Research Portfolio Manager to discuss.

5.2. Co-Investigators

Teams should include up to seven Co-Investigators who will provide significant intellectual input into the Cancer Grand Challenges award, and lead or provide substantial contributions to individual work packages. Proposals to include more than seven Co-Investigators will not be considered.

Co-Investigators may only be listed on one application for this funding call.

Commercial collaborations are encouraged where appropriate. Co-Investigators 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. They will be signatories to the Cancer Grand Challenges Award Agreement, even if a commercial entity will not receive Cancer Grand Challenges funding. Thus, commercial entities and research institutions must be familiar with Cancer Grand Challenges funding terms and conditions, and policies listed in **Section 6**.

5.3. Collaborators

Academic and commercial collaborators providing expertise, services, resources or models are encouraged where appropriate. Please note that, as outside the core funded team, it is not expected that Collaborators will receive funding unless providing an integral contribution to your project.

5.4. Patient Advocate(s)

Applicants must consider opportunities to involve advocates (patients, survivors, caregivers) for people affected by gastroesophageal cancer in their research.

Funded teams will be expected to work with the Cancer Grand Challenges office and its Advocacy Panel to develop a patient involvement and engagement strategy appropriate for their research plans. **If successful, we will provide additional information about patient advocate involvement and engagement.**

5.5. Programme Manager

Funded teams will be required to recruit a programme manager to work full-time on the Cancer Grand Challenges team. Responsibilities could include, but aren't limited to:

- Assisting the Team Lead and Co-Investigators in monitoring and ensuring team compliance with award requirements and meeting milestones;
- Facilitating team communication, as well as communicating frequently and directly with leadership across participating institutions and with the funders;
- Ensuring timely publication of findings, availability of high-quality data and proper IP management;
- Preparing 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.

The application requires you to summarise the structures and processes you will put in place relating to the management and governance of your research. This should include the expected requirements and role responsibilities of the full-time programme manager.

6. Award terms and conditions

Cancer Grand Challenges awards are subject to the terms and conditions, and funding policies, set out in the following documents:

- Cancer Grand Challenges Award Agreement;
- Cancer Grand Challenges Award Management and Funding Policy Guide;
- Cancer Grand Challenges Commercialisation Policy; and
- Cancer Research UK Allowable Costs Guidance.

The terms and conditions, and funding policies, are non-negotiable. The CGC office can assist with questions or concerns relating to the above documents.

6.1. Publicity

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.

6.2. Use of your data

Cancer Research UK will act as the operational manager of the funding call 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 this application with the Torrey Coast Foundation in the United States. The Team Lead will be required to confirm on behalf of each named researcher (or collaborator) on the application that they consent to personal data being shared by Cancer Research UK with the Torrey Coast Foundation, or other relevant funding agencies.

Stricter controls and protections apply to the processing of personal data under UK law (including the General Data Protection Regulations) than generally apply to the processing of data in the United States.

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

7. What we will fund

7.1. Direct research costs

The Cancer Grand Challenges award will provide up to **£25 million GBP** for direct research costs that are verifiable from accounting records. No more than 50% of a team's funding may be issued to institutions in a single country. Please refer to the Cancer Research UK Allowable Costs Guidance and **Section 8.2.3** Finance Schedule for more information.

7.2. Indirect costs

Depending on the composition of funded teams, indirect costs (e.g. costs related to buildings and premises) may be funded for some institutions in geographies where this is standard practice. The UK and most European countries do not use this funding model, so indirect costs in those jurisdictions may not be paid.

Indirect costs will be capped at 10% of the total funding envelope where such costs are applicable, with the total funding envelope (including indirect costs) not exceeding £27.5m over 5 years. The decision to fund indirect costs is at the sole discretion of Cancer Research UK.

Cancer Research UK will not support indirect costs for commercial entities.

8. Written application

Please refer to **Section 1.2.** for an overview of the application process.

If your Letter of Interest (LOI) is deemed eligible and within scope by the Cancer Grand Challenges office, a FlexiGrant full application link will be provided to the lead applicant on Cancer Research UK's grants management system FlexiGrant**,** which will contain the following tabs: 'Participants' and 'Application'.

8.1. Participants

On the 'Participants' tab, please add all team members to the application under 'Research Team'. This will generate an email notification from FlexiGrant, containing a link that will let them accept the participation. Once accepted, they will be asked to complete a diversity monitoring form, confirm their contact details and select their role on the application (e.g. Co-Investigator). Once they have submitted by clicking 'Finish contribution', the Team Lead will receive an email notification, the participant status will read 'Complete', and the contact will have read-only access to the application form.

You may also add one administrative assistant to the application to assist with your submission under 'Application Support'.

8.2. Application

8.2.1. Research Abstract

Applicants are required to provide a publishable research abstract, which must not include any figures or graphics. The abstract may be used on the CGC website, to help Cancer Research UK's fundraising activities, and for other purposes, thus should not include any confidential information.

8.2.2. Research Proposal

The Research Proposal must not exceed **10 pages**. Throughout your proposal, where applicable, please indicate which work package(s) (WPs), investigators and institutions are involved in the research being described, e.g. "the samples will be analysed (WP3, Smith, Cambridge)". Figures and infographics may be embedded within the proposal where they support and help illustrate the research plan. To ensure readability, applicants should use a minimum font size of 10, present clear, accessible visuals and avoid overly complex or data-dense figures containing small text or difficult-to-read graphics. Please ensure that all pages are numbered.

1. What's the vision and how does it address the challenge?	Briefly describe: • the vision for your proposal and how it addresses the cancer grand challenge you are applying to tackle. • the potential impact of the research and how it will remove barriers or transform the field. • how the scope and scale of your proposal will allow for unique and innovative approaches that are not otherwise possible via other funding mechanisms.
2. What are the critical research objectives that will deliver your vision?	• Outline the team's key objectives. Objectives may be met through a set of interconnected work packages that cut across different investigators and institutions. • Demonstrate the integration of the team's objectives and the coherence of the entire proposal by outlining how individual work packages fit together. For each objective, what are the main hypotheses or key lines of investigation? • Clearly describe the hypotheses/key lines of investigation you will follow, any pertinent evidence to support your hypotheses, and the critical experiments and research approaches over the course of your programme. Please provide more details particularly with regards to the early stages (years one & two) of the proposed research, recognising that the latter years are likely to evolve. Include evidence to support the feasibility of these approaches.
3. What will your outputs be? How will these inform the team's direction?	• Describe the expected outputs and outcomes of the research both for the individual work packages and the overall team and demonstrate how outputs from each work package will be used to inform experimental design across the team as the work progresses. • You may find it easiest to include this as a programme timeline and/or Gantt chart with clear milestones, measurable/quantifiable where appropriate (recognising that years one & two will be better developed than the outer years). • Summarise in no more than two paragraphs what the future of the field looks like if you are successful in your research programme.
4. Translation and impact	The ambition of this funding call is to generate discoveries with the potential to deliver significant long-term global benefit for patients with gastroesophageal cancers and/or the wider public. Applicants should: • Articulate credible pathways to translation in detail, where appropriate, recognising that meaningful improvements in cancer prevention, diagnosis and treatment are often enabled by transformative mechanistic discoveries.
5. What challenges or interdependencies are there? What contingency plans are in place?	• Highlight major potential challenges or interdependencies between work packages that could impact on the team's overall ability to address the challenge and suggest how you would approach them with alternative plans.

6. Data architecture and AI strategy	Applicants should describe how data will be generated, managed, integrated and leveraged throughout the programme. This should include: • An overview of the proposed data architecture, including data and metadata standards, governance, interoperability, sharing and long-term stewardship. Further information on data sharing may be provided in the appendix. • Plans to establish data repositories, metadata frameworks and, where relevant, biorepository infrastructure **within the first six months of the award**, ensuring data and samples are generated, stored and shared according to agreed standards and can be effectively reused. • The team's AI strategy, including how advances in AI and agentic AI may support discovery, hypothesis generation, experimental design, data integration and interpretation throughout the programme. Teams are encouraged to familiarise themselves with emerging AI-enabled scientific platforms, including Project AURORA and ToolUniverse, where appropriate.
7. How will the team be managed?	Describe how you will manage your team. This should include: • A summary of management and governance structures and processes, including decision-making procedures.

List all references at the end of the proposal including authors, publication year, title and journal name, volume, page numbers (don't use shortened references, i.e. 'et al.'). Number your references in the order in which they appear in the text listing them in Vancouver style. References are not counted in the page limit.

Using generative Artificial Intelligence tools when building your full application

If using generative Artificial Intelligence (AI) in developing your application, teams must:

- Support the highest levels of research integrity as set out in Section 3.2.4 of the Award Management and Policy Guide.
- Support the highest levels of research integrity as set out in Guidelines for research conduct.
- Use generative AI tools responsibly to ensure the originality, validity, reliability and integrity of outputs created, and in accordance relevant legal and ethical standards, including data privacy.
- 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.

8.2.3. Finance Schedule

In the Finance Schedule template, you are asked to input high-level costs requested as part of your Cancer Grand Challenges application. Costs must be provided in pounds sterling (GBP), and the overall team budget may not exceed £27.5m (total award, including indirects if applicable).

Within the Finance Schedule, separate tabs should be populated for each participating institution. Each institution's budget should be broken down by year of award (total of 5 years), under the following categories:

Category	Information required
Personnel	• Name of staff member (or TBC if pending recruitment) • Job title • Basic salary (If an institution does not pay fringe benefits, please explicitly state this by inputting 0%, rather than leaving the fringe field blank) • % effort FTE (entered in 0.00 format) • Brief description of the role, and the work package(s) on which the individual will be working
Lab consumables	• Description of consumables required for each staff member • Justification for any request of more than £17,500 per full-time staff member
Institutional (core) services	• Description of services required • Short narrative justification with key calculations
Clinical costs	• Detailed description and justification with key calculations
Animal costs	• Description and justification of costs, with key calculations including number of animals, cost per cage, husbandry, etc.
Student fees	• Description of role and explanation of cost per student
Equipment	• Description of purpose on the Cancer Grand Challenges award and justification for purchase • A recent quote for any equipment purchase over £25,000
Computing costs	• Description of computing costs
Travel costs	• Description of travel costs
Sub-awards	• Justification for requiring sub-award, description of costs
Other costs	• As required • Discretionary funds (Team Lead schedule only)

Please refer to Section 3.1 of the Award Management and Funding Policy Guide when building your budget.

Applicant teams should only include indirect costs in their Finance Schedule under the 'Other costs' section for each individual Host Institution.

Teams will have an annual opportunity to reprofile their budgets, subject to successful annual review and approval from the funder(s).

Teams must leave at least 10% of their overall budget unallocated as a 'discretionary fund' to support emerging lines of scientific investigation in outer years of the award, not anticipated at time of application. Discretionary funds should be evenly distributed across years 3-5 (i.e. not disproportionately allocated across one or two years). Discretionary funds should be included under the 'Other costs' section of the Team Lead's host institution, although the expenditure may end up being incurred by other participating institution(s). The allocation of 10% discretionary funds to the TL's Finance Schedule will be excluded from calculations relating to the requirement that no more than 50% of the total award budget is allocated to a single country.

Annual reprofiling of budgets and subsequent allocation of the discretionary fund may not result in more than 50% of the Cancer Grand Challenges funding being distributed to institutions in one country throughout the lifetime of the award.

8.2.4. Appendix

In order to ensure Research Proposals comply with Section 3 of the Award Management and Funding Policy Guide (see **Section 6**), we require an appendix that includes details of:

- Any animal work;
- Any work involving human subjects;
- Statistical analyses and experimental design;
- Data and sample sharing;
- Intellectual Property;
- Select agent research.

The appendix must not exceed **10 pages** and there is no individual page limit for each section of the appendix. No appendix template is provided – you may use a format best suited to your application. Throughout your appendix, where applicable please indicate which work package(s) (WPs), investigators and institutions are involved in the research being described, e.g. "the samples will be analysed (WP3, Smith, Cambridge)". In your appendix, use the subheadings below and number all pages.

Animal studies

Your appendix should include:

- Description of proposed procedures,
- Justification of proposed studies
- And the Host institutions at which animal studies will be conducted

Animal studies must adhere to all relevant local regulatory systems. Welfare standards must be consistent with UK standards, even where the funded research is to be performed outside of the UK. A list of relevant expected standards can be found in the Cancer Grand Challenges Award Management and Funding Policy Guide.

Description of proposed procedures

Provide a concise description of all proposed procedures on live animals and describe the animals to be used. Include details of the animal species; strains; ages; sex; and the total number of animals to be used by species.

Please confirm that you will not use toe clipping and/or tail biopsy for identification or genotyping purposes or justify why this is required.

Justification of proposed animal studies

Provide a justification for the use of animals in the proposed research as per the NC3R guidelines. This section should:

- Provide rationale for the experimental design including choice of species;
- Outline, if new models will be developed and why this is necessary
- Include the efforts that will be taken to address the principles of the 3Rs with specific examples
- Confirm that the methods of euthanasia (humane killing) adopted are in line with those recommended by, or permitted under, Directive 2010/63/EU. Please contact the research office if you are proposing to use a method of euthanasia that is not consistent with these guidelines.

Human subjects

Provide a brief summary explaining and justifying any activities involving human subjects, e.g. prospective sample collections; epidemiological studies; or clinical research.

For any clinical development activity, please include:

- Status of any drugs, tools or technologies to be used in the study (whether these require development/manufacture of novel agent(s));
- Trial design (include main inclusion/exclusion criteria, summary of treatment(s), identify control arm and justify choice of experimental arm(s). For complex designs attach separate trial flowchart/diagram);
- Primary, secondary clinical endpoint(s);
- PK/PD, safety efficacy, imaging endpoints;
- Research endpoint(s);
- Host institutions at which human studies will be conducted.

If selected for funding, more information on your proposed human subjects research will be required and may be subject to further review.

Statistical analyses and experimental design

Please provide justification for the design of critical experiments including molecular, animal and human studies. You may wish to incorporate this in your animal studies and human studies sections.

This should include an overview of the experimental approach summarising:

- An explanation of how effect sizes have been calculated and a justification of their biological relevance;
- The power calculations used to determine your sample size (or a principled explanation of an alternative basis for calculations, justifying why you haven't used statistical calculations);
- An overview of the planned statistical analyses in relation to the sample size and list any statistical advice sought/available.

Sample and data sharing within teams

Ensuring the legal framework/agreements to enable samples and data to be shared across teams is critical to the success of a programme. Discuss how you propose to address this to ensure that a strategy is implemented early in the programme.

Data sharing beyond the team

Investigators must submit a data sharing plan that outlines how underlying data for each publication of results will be made broadly available within two months for academic non-commercial research purposes through an appropriate data repository (such as the Genomic Data Commons or dbGaP) while:

- Protecting confidential and proprietary data (and may include restrictions to access based on the commercial nature of research proposed to be conducting using such data);
- Safeguarding the privacy of participants through pseudo or anonymisation.

This data sharing plan should include, to the best of your current knowledge, your expectations and aims relating to:

- The expected volume, type, content and format of the final dataset;
- The expected standards that will be utilised for data collection and management;
- Expectations relating to data sharing mechanisms for academic non-commercial research, including estimated timescales for public release of the data and the repositories where data is expected to be deposited;
- Expectations as to the sharing strategy for commercial organisations and how you will ensure the long-term sustainability of the dataset.

Teams are encouraged to speak to the Cancer Grand Challenges office team for support in building this part of their applications. If selected for funding, more information on your plans for data sharing will be required. The Cancer Grand Challenges office team, working in conjunction with Cancer Research Horizons, can help support the creation of data collection, generation and sharing strategies that maximise the long-term value of the data for secondary use both commercial and academic and we encourage you to engage as early as possible with this team.

Intellectual Property

Please provide a summary of the competitive position and commercial attractiveness of your proposal:

- What IP, data and/or know-how do you expect to generate, and what strategies do you have to manage it?
- Where appropriate, what is your proposed commercialisation strategy?
- What is the competition in the area?
- Are you aware of any patents that could affect the development of your project?
- Are you aware of any freedom to operate issues?

Teams are encouraged to speak to the Cancer Grand Challenges office team for support in building this part of their applications.

Select Agent Research

Describe details of any select agents to be used in the proposed research. Select agents are biological agents and toxins that have been determined to have the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal or plant products. Include: 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s), as appropriate.

8.2.5. Biosketch upload

Each team is required to upload a completed Biosketch for the Team Lead and all Co-Investigators. Each Biosketch may not exceed **one page**. A template is provided via FlexiGrant.

8.2.6. Schedule of Background Intellectual Property

Applicants must provide a full list of any Background IP (including prevailing third-party rights or encumbrances) needed to deliver the proposed research by each participating institution. Applicants must confirm all Background IP can be used in accordance with the Commercialisation Policy (see **Section 6**). A Schedule of Background Intellectual Property template is provided via FlexiGrant and will be included as Schedule D in the Award Agreement signed by all participating institutions and the funder(s).

8.2.7. Letters of Support

Teams are required to obtain letters of support from all participating institutions confirming they can and will adhere to the Cancer Grand Challenges terms and conditions, and policies (see **Section 6**). The following Letters of Support should be uploaded and submitted with the FlexiGrant application.

Letters of support from the Host Institutions of all Co-Investigators	A letter on headed paper from a person or persons at each Co-Investigators' Host Institution who has or have the authority to confirm approval of the relevant investigator/investigators' participation in the proposed Cancer Grand Challenges research. The signatory or signatories should be the Host Institution Administrator under the definitions provided in Section 1.2.2 of the Award Management and Funding Policy Guide. The letter should confirm that: • The institution has read and understood the contents of the Cancer Grand Challenges Award Agreement, Award Management and Funding Policy Guide, commercialisation policy and Cancer Research UK allowable costs guidance – and is ready to sign the Award Agreement if the application is recommended for funding. • The application has been submitted with the agreement of the host institution and that, if funded, the award will be used only to support the approved Cancer Grand Challenges research. • The host institution is not aware of any relevant information that has been withheld or of any information given in the application that is misleading. • It is the intention of the institution to maintain support for the Co-Investigator's department(s) during the proposed award.
Letters of support from any collaborators or commercial partners	Where applicable: • Letters from collaborators detailing their participation • Letters of support from commercial or academic partners contributing gift-in-kind reagents, pharmaceutical agents, technology, services or expertise critical to the research

If the required Letters of Support are not provided within your application and/or do not meet the stipulations as outlined in the table above, this may impact your application's eligibility to be shortlisted and ultimately funded.

9. Challenge Articulations

9.1. Overarching context and unmet need

Gastric cancer, oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma (gastroesophageal cancers) are major causes of cancer mortality. Outcomes remain poor, in part because these cancers are commonly diagnosed after they have become locally advanced or metastatic, when treatment is already less likely to succeed. Despite their lethality and substantial unmet need, progress to understand their biology, and to prevent, detect, diagnose, and treat has been limited compared with many other types of cancer.

The burden of gastroesophageal cancers varies markedly across the world. Gastric cancers are especially common in East Asia, Eastern Europe and parts of South America. Oesophageal squamous-cell carcinoma

reaches exceptionally high incidence across regions of East Africa, Iran and China. By contrast, the incidence of oesophageal adenocarcinoma has risen markedly over recent decades in many high-income Western populations. These striking differences point to important but poorly understood interactions between inherited susceptibility, infections and environmental exposures, tissue biology and host responses.

Gastroesophageal cancers are biologically distinct diseases and do not follow a single trajectory. Some likely arise through sequential tissue changes leading to metaplasia, dysplasia and eventually cancer. Others may not follow a clearly defined precursor pathway. In both cases this is likely due to persistent exposure, tissue injury, inflammation and altered regeneration. In addition, even where risk factors and precursor conditions are recognised, they do not reliably determine outcome. Histologically normal oesophageal squamous epithelium can contain extensive somatic clones carrying mutations in cancer-associated genes without progressing to malignancy. Furthermore, although *Helicobacter pylori* infection is a major risk factor for gastric cancer, only a minority of infected people develop the disease. Similarly, only a minority of people with Barrett's oesophagus progress to oesophageal adenocarcinoma.

Conversely, many people who develop gastroesophageal cancer were not previously recognised as being at high risk. This is particularly important in oesophageal adenocarcinoma, where a high number of cancers are diagnosed outside established Barrett's oesophagus surveillance programmes.

These observations suggest that exposure, mutational burden, clonal expansion and histological abnormality alone cannot explain who progresses to cancer. Progression may depend on interactions between the cell of origin and its state, tissue architecture, inflammatory and regenerative memory, clonal competition, immune surveillance, stromal and microbial ecosystems, ageing, inherited susceptibility and environmental exposures.

Recognising the urgent need for progress, Cancer Research UK and the Torrey Coast Foundation have partnered to launch a targeted Cancer Grand Challenges funding call on gastroesophageal cancers and seek to fund international teams capable of bringing novel approaches, technologies and thinking to tackle two major challenges.

9.2. CHALLENGE 1: Gastroesophageal transformation into cancer

UNDERSTAND AND REVERSE EARLY TISSUE CHANGES LEADING TO GASTROESOPHAGEAL CANCERS

CONTEXT

Oesophageal and gastric adenocarcinomas can develop over years through persistent exposure, tissue injury, inflammation, altered regeneration, metaplasia and clonal selection and outgrowth. This prolonged

development may create a window in which early disease can be detected and cancer prevented before it becomes invasive and increasingly autonomous.

Metaplastic tissue can regress, but repeated cycles of injury, regression and re-emergence may act as a biological ratchet, progressively stabilising abnormal cell states and increasing the likelihood of dysplasia. Genetic or epigenetic alterations may subsequently reinforce these states and reduce their dependence on the signals that initiated them. Understanding and manipulating this continuum could enable early tissue changes to be restored to normal, while more advanced abnormal states might be eliminated, durably controlled or redirected into terminal, non-malignant fates.

The cells from which these cancers arise, the epithelial states they adopt and the immune, inflammatory, stromal and microbial processes that initiate, sustain or constrain their progression remain incompletely understood. Different oesophageal adenocarcinomas may also follow distinct trajectories. Furthermore, many oesophageal adenocarcinomas are diagnosed in people who were not previously diagnosed with Barrett's oesophagus.

CHALLENGE

This challenge seeks to define the biological mechanisms that initiate, sustain and drive the progression of early oesophageal and gastric adenocarcinomas, and to use this understanding to determine whether early tissue changes can be reversed, durably halted or redirected away from malignant progression.

Note that this challenge excludes investigating the transition to, and from, Barrett's oesophagus, recognising the large number of spontaneous oesophageal adenocarcinomas that appear to arise in the absence of Barrett's.

Potential questions that could be addressed by teams include, but are not limited to, identifying the cell of origin of oesophageal and gastric adenocarcinomas, the biological mechanisms that drive their initiation, and the influence of ageing, environmental exposures, and immune responses on these processes.

Applications should focus on early tissue change en route to tumour initiation to develop a deeper understanding of disease risk for future prevention programs. Studies of established cancer or experimental models of established cancer may be included where they directly illuminate the initiation of early human disease. Teams are encouraged to develop enabling technologies where existing approaches cannot identify, reconstruct or manipulate the relevant biological transitions.

If clear biological mechanisms are identified which govern initiation and progression, teams may seek to reverse them. Potential approaches might include but not be limited to restoring normal differentiation,

reversing inflammatory or epigenetic memory, disrupting essential tissue dependencies, activating protective immunity or redirecting abnormal cells away from malignant progression.

IMPACT

Solving this challenge could reveal biological mechanisms driving early changes in gastroesophageal cancers and therefore provide an opportunity to shift the management of gastroesophageal cancers from surveillance, ablation and radical treatment towards active biological prevention.

9.3. CHALLENGE 2: Global variation in gastroesophageal cancer

DETERMINE THE BIOLOGICAL MECHANISMS UNDERPINNING GEOGRAPHICAL VARIATIONS IN GASTROESOPHAGEAL CANCER INCIDENCE

CONTEXT

Gastric cancer, oesophageal adenocarcinoma and oesophageal squamous-cell carcinoma display profoundly different geographical patterns of incidence. Oesophageal squamous-cell carcinoma reaches exceptionally high incidence across regions of East Africa, Iran and China. Gastric cancer is especially common in East Asia, Eastern Europe and parts of South America , while oesophageal adenocarcinoma has risen markedly in many high-income Western populations.

Known risk factors explain only part of this variation. *Helicobacter pylori*, tobacco, alcohol, reflux, obesity, diet and nutritional status and inherited susceptibility contribute to gastroesophageal cancer risk but do not fully account for the magnitude, distribution or changing incidence of these diseases. Decades of research into individual risk factors have not completely explained the biological mechanisms behind the contrasting global patterns of the three major gastroesophageal cancers.

CHALLENGE

This challenge seeks to move beyond descriptive epidemiology and establish the biological mechanisms through which regionally patterned exposures and host factors shape gastroesophageal cancer risk. Relevant factors could include environmental and occupational exposures (including during critical periods of life), infections, nutrition, metabolism, microbial communities, inherited susceptibility, immune fitness, tissue injury and repair, normal epithelial clonal dynamics, social determinants and sex-related biology. These examples are illustrative rather than prescriptive.

Geographical variation should be used as a natural experiment through which causal mechanisms can be distinguished from correlates of disease. Teams should integrate population-level observations with mechanistic investigations, building a “molecular epidemiological” case to determine how relevant

exposures or host factors alter progenitor cell states, tissues and early disease trajectories. Comparing the three major gastroesophageal cancers may reveal shared mechanisms of early tumour initiation, or distinct causal pathways or factors with opposing effects across cancer types, therefore teams may choose to investigate more than one type of cancer. Teams will also need to account for differences in cancer registration, diagnostic access, anatomical and histopathological classification, and sampling issues.

Purely descriptive incidence mapping, studies of isolated candidate exposures without a route to causal understanding of early cancer initiation, or molecular profiling disconnected from population patterns will not be sufficient. Teams are encouraged to develop novel technologies where existing approaches cannot measure relevant exposures, reconstruct tissue histories or establish biological causation. Such technologies should be appropriate for use across participating regions.

Addressing this challenge will require international teams to collaborate across countries with contrasting incidence, exposures and disease subtypes. Teams should be co-developed by investigators across participating regions. Scientific leadership, governance, experimental work and analysis of samples and data should be shared across the partnership. The challenge should not solely rely on the extraction of samples to a small number of established research centres.

VISION AND IMPACT

Solving this challenge could explain major global differences in incidence at a biological level and provide a mechanistic foundation for locally appropriate prevention strategies.

10. Contact details

For enquiries relating to this funding call, please find contact details of CGC personnel below.

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