IN FOCUS

Introducing Five New Cancer Grand Challenges Teams

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Summary: Cancer Grand Challenges is an international funding initiative that aims to unite the world's best scientists to tackle some of cancer's toughest problems by funding team science on a global scale. Here, we discuss the five newly funded teams and the challenges they will address over the coming years.

INTRODUCTION

Each year, 17 million people around the world are diagnosed with cancer. Millions of people die from cancer annually, and these numbers are rising. If this increase remains unchecked, by 2040, 27.5 million people worldwide are predicted to be diagnosed with cancer every year (Cancer Research UK, https://www.cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer). A recent report from the American Cancer Society has projected that 611,720 people will die from cancer in the United States alone in 2024 (1).

Decades of research, and the application of increasingly sophisticated technologies that allow cancer to be investigated at a molecular and cellular level in real-time, have given us a deep understanding of many aspects of how cancers are initiated, develop, and metastasize. This understanding has been translated into prevention strategies and therapies, and consequently many cancers, when detected early, are now treatable and five-year survival rates for some cancers now exceed 90% (National Cancer Institute, Surveillance, Epidemiology, and End Results Program https://seer.cancer.gov/report_to_nation/statistics.html). However, despite this progress, many complex challenges – some new and some that have confounded researchers for decades – remain unsolved and continue to impede progress. To make progress against these challenges, we need interdisciplinary endeavors, international collaboration, and long-term commitment. We need team science on a global scale. Cancer Grand Challenges (Cancer Grand Challenges, https://cancergrandchallenges.org/) was established to deliver just this.

Founded in 2020 by Cancer Research UK and the US National Cancer Institute, Cancer Grand Challenges aims to make progress against complex cancer research problems by fostering a shift in how team science is conducted. To identify the most complex challenges, we engage the global cancer community: we solicit ideas from across the research and advocacy communities, and our scientific leaders then select challenges with the greatest potential benefit for patients and the public.

Last year in *Cancer Discovery*, we outlined our most recent round of challenges (2). In response to this funding call, we received 176 Expressions of Interest from many outstanding teams, proposing innovative and exciting approaches to tackle our challenges. Our scientific leaders selected 12 of these teams to submit a full application. And after a rigorous selection process, we are now delighted to reveal the five successful teams – more teams than we have ever awarded in a single funding round. Each team will now receive Cancer Grand Challenge Awards (up to $25m) to pursue its research.

T-CELL RECEPTORS: TEAM MATCHMAKERS

T cells are central players in the immune response, and harnessing their power in the development of immunotherapies is transforming the treatment landscape for some cancers. However, despite the clinical success of immunotherapies, their effects are not universal across cancer types and patient subsets.

Understanding how T-cell receptors (TCR) recognize tumor antigens presented by MHCs is critical to understanding how the immune system functions, and to realize the full potential of antigen-specific immunotherapy. To achieve this goal, a quantum leap forward is required. This challenge offered the opportunity to address this problem by bringing together recent advances in machine learning with the expertise of structural biologists, immunologists, and computational biologists, with the aim of developing an approach to predict which antigens TCRs recognize. This prediction model could ultimately be used to improve the clinical effectiveness of future cancer immunotherapies.

Team MATCHMAKERS, led by Professor Michael Birnbaum (Massachusetts Institute of Technology, Cambridge, MA), will tackle this challenge. The vision of this interdisciplinary team is to strive for a reality in which determining TCR specificity in a clinical setting can be accomplished with a routine tumor biopsy or blood test coupled with computational predictions.

Decades of research, including landmark studies by members of team MATCHMAKERS, have produced a detailed mechanistic understanding of how TCRs are generated, recognize antigens, and induce effector responses to control disease (3, 4). The molecular basis of peptide MHCs (pMHC) recognition by TCRs is central to this challenge and will be a key focus for the team. Structural studies of TCR–pMHC complexes have revealed that despite the broad sequence diversity of both TCRs and peptide antigens, TCRs generally engage pMHCs in a relatively restricted range of docking orientations (5). Understanding and then applying the rules

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governing TCR–pMHC interactions will also be a key focus for the team.

Recent advances in machine learning have enabled impressive progress in computational protein structure prediction (6). However, despite interest in applying novel computational approaches to predict antigen recognition by TCRs, progress has not yet been practically useful. Team MATCHMAKERS posits that the principal obstacle to computational prediction of TCR–pMHC interactions is a lack of training data. To move beyond what is currently possible in terms of predicting TCR–pMHC interactions, team MATCHMAKERS will generate new sequence, structure, and structure–activity relationship datasets that are sufficiently scaled to train new algorithms. It will develop new experimental approaches to enable such data collection and devise computational approaches that account for the unique considerations of TCR-pMHC binding and structure.

This is a considerable undertaking, but if the team succeeds, insights gained will have implications beyond cancer, for example in infectious disease, autoimmunity, and allergy.

EARLY-ONSET CANCERS: TEAM PROSPECT

Over the last decade, evidence has emerged to demonstrate a marked increase in the incidence of some cancers in adults under 50 years of age. The incidence of early-onset cancers (EOC) has increased in multiple countries, and the rise cannot be explained by germline genetic alterations or increased screening. EOCs contradict the accepted relationship between aging and cancer, and risk becoming an epidemic in the future.

To address the emerging issue of EOCs, we need to understand the mechanisms linking lifetime exposures in multiple cancer types to cancer initiation. Addressing this challenge requires a robust understanding of the mechanisms underpinning the biological and environmental causes behind the emerging global phenomenon of EOCs. This knowledge could then be used to develop preventative measures, thus protecting populations at risk.

Professor Andrew Chan (Massachusetts General Hospital, Cambridge, MA) and Dr Yin Cao (Washington University in St. Louis, St. Louis, MO) are leading team PROSPECT (Pathways, Risk factors, and mOlecuIeS to Prevent Early-onset Colorectal Tumours), an international group of experts who plan to address the global rise in the incidence of early-onset colorectal cancer (EOCRC). The team's vision is to unravel the intricate network of causal factors that disrupt biological homeostasis to promote EOCRC over the course of a person's life, with the ultimate aim of reversing it.

The team highlights the critical need to identify novel, reproducible, biologically meaningful risk factors for EOCRC. The concept of the exposome was first introduced by Christopher Wild in 2005 and is defined as encompassing "every exposure to which an individual is subjected from conception to death." (7). This definition emphasizes the need to consider both the nature of exposures and their temporal variations. However, reliably delineating the exposome across an individual's lifespan in relation to disease outcomes during adulthood poses substantial challenges arising from limitations in the measurement of exposures, to the suitability of computational approaches to infer individual exposures accurately and meaningfully. Furthermore, while environ-

mental epidemiology studies centered on location-based data have achieved notable advancements (8), studies focused on EOCRC are limited. In addition, studies from the Cancer Grand Challenges' Mutographs team have highlighted the substantial challenges that using genomic signatures to identify exposures continues to present (9, 10).

Team PROSPECT will implement a comprehensive approach that will leverage epidemiologic cohorts with rich biospecimen collections, combined with molecular discovery, ultra-deep genomic and microbiome sequencing, as well as animal models to investigate novel exposure identification for EOCRC. The team aims to elucidate the lifelong impact of established and novel risk factors in the rising incidence of EOCRC and characterize the causal mechanisms underlying specific risk factors throughout the life course for EOCRC, by understanding how risk factors perturb physiology to result in long-term susceptibility to cancer.

The relatively low incidence rate of EOCRC means that scale is important; team PROSPECT will bring together an impressive cohort of approximately three million subjects to tackle this problem. This colossal undertaking could lead to the insights required to develop mechanistic and contextual-based precision prevention strategies that will deliver near-term benefits to younger generations worldwide.

CANCER INEQUITIES: TEAM SAMBAI

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

While most inequities are likely the consequence of social determinants and circumstances, such as late-stage diagnosis due to inadequate access to health care, there are emerging data that indicate genetics and biology also play a critical role. Polygenic scores may be useful indicators of risk that vary by self-identified race and ethnicity (SIRE); genetic ancestry is correlated with cancer risk or outcomes independently of SIRE; and tumor phenotypes and mutational signatures differ by SIRE. As the relative contributions of genetic, biological, and social drivers of cancer etiology remain unclear, approaches aimed at reducing inequities remain inadequate.

This challenge aims to generate functional and mechanistic insights into cancer inequities by generating new trans-disciplinary approaches and applying them in diverse populations. This should lay the groundwork for the development, evaluation, and implementation of future prevention, early detection, and treatment strategies to achieve equity in cancer outcomes across all sections of society.

Team SAMBAI (Societal, Ancestry, Molecular and Biological Analyses of Inequalities), led by Professor Melissa Davis (Morehouse School of Medicine, Atlanta, GA), will address the Cancer Inequities challenge. The team will focus on the global African diaspora and will study three cancer types all with a disproportionately higher rate of aggressive tumour grade and early onset in black patients: prostate, breast, and pancreatic cancers. For example, racial disparities in cancer risk and outcomes are stark, with black women being 2.7 times more likely to be diagnosed with triple-negative breast cancer and black men twice as likely to die of prostate cancer, compared with age-matched white cohorts (11).

A crucial step in reaching cancer equity is understanding fully all aspects of the drivers of disparities, from environment to biology. This team is uniquely poised to address this challenge since members of the team have pioneered the investigation of genomics in cancer disparities research, and over the past two decades have uncovered evidence of distinct immunological mechanisms associated with genetic ancestry. Team SAMBAI members have also developed methods to quantify environmental exposures and interrogate the lived experiences of marginalized populations and how these manifest biologically.

Team SAMBAI will bring together scientists across Africa, Europe, and North America, and aims to build an unprecedented resource, the SAMBAI Biobank and Data Repository for Cancer Equity Research. This repository will comprise a comprehensive, accurate and relevant measurement of social, environmental, genetic, and immunological factors and drive an integrated set of analyses to define the causal relationships of disparate outcomes in diverse populations. In doing this, the team plans to establish a sustainable framework for team science approaches with under-represented partners and establish best practices for coordinating cancer equity research on a global scale. The SAMBAI data resource should help inform novel trial designs to ensure that specific genomic and immunological features become a routine component of precision theragnostic oncology.

SOLID TUMORS IN CHILDREN: TEAMS KOODAC AND PROTECT

Cancer remains the leading cause of death by disease in children globally. Outcomes for some pediatric cancers have not improved in more than 30 years, and progress in the treatment of some solid tumors in children, for example brain tumors, has largely stalled. Furthermore, in children who relapse, there are limited treatment options available meaning their outlook is often poor.

We need innovative interventions that specifically target the unique biology of pediatric tumors, which are often driven by oncogenic fusions and other pediatric-specific oncoproteins that have historically been considered "undruggable." However, with recent advances in targeted protein degradation and chemical interventions to inhibit protein–protein interactions, it has recently become possible to target these oncoproteins.

This challenge called for a disruptive, collaborative approach to apply these novel technologies to target oncogenic drivers in children's solid tumors, with the ultimate aim of improving survival and reducing the lifelong toxicities experienced by survivors of these diseases.

Two teams have been funded to take on this challenge, teams KOODAC, led by Professors Yaël Mossé (Children's Hospital of Philadelphia, Philadelphia, PA) and Martin Eilers (University of Würzburg, Germany), and PROTECT (Harnessing PROTEin degradation for advanced Childhood Tumours), led by Professor Stefan Pfister (Hopp Children's Cancer Center, Heidelberg, Germany). Both teams bring together international groups of world-leading experts in pediatric oncology and drug discovery, including targeted protein degradation, high-throughput chemical screening, medicinal chemistry, structural biology, tumor biology, preclinical drug testing, and clinical trials. Their overarching vision is to develop drugs that will become the new standards of care for children with solid tissue malignancies. The teams will work across multiple diseases including Ewing sarcoma, neuroblastoma, medulloblastoma, fibrolamellar hepatocellular carcinoma, rhabdomyosarcoma, synovial cell sarcoma, high-grade glioma, ependymoma and gastrointestinal stromal tumors, and their relevant drivers/targets/oncogenic events. There are both unique and shared targets, but each will use different drug discovery and development approaches.

Guided by biology and the specific biological roles of key driver proteins in these diseases, team KOODAC will focus on MYCN, EWSR1-FLI, DNAJB1-PRKACA, ALK, and PAX3/PAX7-FOXO1. The team aims to develop novel orally bioavailable drugs that are blood–brain barrier penetrant. Targeted protein degraders have a high therapeutic index and would enable children worldwide to benefit from their reduced toxicity. The team will focus on the clinical development of compounds based on their safety, efficacy, and pharmacokinetic/pharmacodynamic properties, and on understanding resistance mechanisms.

Team PROTECT will focus on targets in Ewing sarcoma, neuroblastoma, synovial sarcoma, ependymoma, and high-grade glioma. It will use novel approaches to target previously thought to be undruggable pediatric drivers/dependencies in these diseases, to overcome resistance to available targeted inhibitors, and to improve the efficacy and therapeutic window of chimeric antigen receptor T-cell treatments. Ultimately, it is the team's ambition to establish a sustainable platform for repeated developmental cycles of pediatric-specific drug discovery for emerging targets including developing a viable financial model to derisk drug candidates for rare pediatric tumors.

Compounding the biological challenges, drug development in biopharma for pediatric solid tumors has often not been prioritized due to the small market size. Cancer Grand Challenges is now funding three teams focused on improving the treatment of children's cancers. If these teams deliver novel therapies for application in clinical trials, this will be a significant step forward in treating cancer in children.

CONCLUSION

Our robust selection process has given us five exciting teams that we hope will contribute significantly to the transformative progress against cancer we are striving for.

These five teams will join our community of researchers and advocates that now extends over 16 countries. The teams will become members of a community in which new technologies are developed and shared; the data generated to tackle one challenge are applied to make progress in another; future research leaders collaborate worldwide; and patient advocates are engaged to ensure that our work benefits from the lived experience of people affected by cancer.

By galvanizing the international scientific community and giving Cancer Grand Challenges teams the freedom to innovate, we aspire to make progress against cancer's toughest research problems. We wish our five new Cancer Grand Challenge teams every success in their efforts to do just that.

Authors' Disclosures

No disclosures were reported.

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