IN FOCUS

Cancer Grand Challenges: Embarking on a New Era of Discovery

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Summary: Cancer Grand Challenges is a unique funding platform that dares global, multidisciplinary teams of researchers to come together, think differently, and tackle some of the toughest challenges in cancer research. Here, we discuss the nine intractable challenges currently open for application.

INTRODUCTION

With the development and approval of many new therapies based on a deep biological understanding of cancer, recent years have seen significant progress against the disease, including for cancers that were previously hard to treat. These hard-won gains, enabled by important insights from decades of science, have taught us a great deal—about cancer and about cancer research. Despite these advances, some difficult problems remain. These range from gaps in our fundamental understanding of basic biological processes and phenomena which have confounded us for years, such as tumor cell dormancy, to global public health issues where evidence is limited and fragmented.

Cancer Grand Challenges is a new global research platform to address these difficult but critical challenges in cancer research. Uniting Cancer Research UK and the U.S. National Cancer Institute, the initiative supports multidisciplinary science on a global scale. By leveraging our combined resources and building on a global foundation of excellence in cancer research, together we can go further than we could independently.

Together, we recently launched nine new challenges, inviting global, multidisciplinary teams to apply. Some, such as the “Inflammation” challenge, look to answer questions that have impeded progress for many years. Others, such as the “Normal Phenotypes” challenge, seek to capitalize on relatively recent yet significant observations that could unlock new thinking about how cancer develops.

Below, we set out the nine new challenges. By driving progress on all nine through the power of global scientific collaboration, Cancer Grand Challenges offers the potential to benefit entire scientific fields.

EXTRACHROMOSOMAL DNA

The idea that genes can be found on extrachromosomal DNA (ecDNA) is not new, but our appreciation of its importance in cancer is growing.

Although ecDNA was discovered in 1965, it took more than a decade for Alt and colleagues to move the field beyond phenomenology, with their discovery that tumor cells could develop resistance to methotrexate via the amplification of the DHFR gene on ecDNA elements (1).

Oncogenes were reported to reside on ecDNA in the 1980s (2), and oncogene amplification was then shown to occur on ecDNA, the frequency and amplitude of which can be altered by different stimuli. Jump forward to the application of high-throughput sequencing, and we now know that oncogene amplification on ecDNA occurs frequently, increasing extreme copy-number variation due to the unequal segregation of circular amplicons, thereby accelerating intratumoral heterogeneity (3).

Although it is becoming increasingly clear that ecDNA promotes aggressive tumor behavior, therapy resistance, and poorer survival, gaps in our knowledge about the origins, evolution, genomic organization, and clinical impact of ecDNA in human cancer remain. Therefore, this Cancer Grand Challenge represents an opportunity to enhance our fundamental understanding of ecDNA—its formation, its role in tumor evolution and clonal dynamics, how it mediates drug resistance, and whether it can be targeted, which will be crucial to address its clinical implications.

SENESCENCE

Hayflick first described the limited replicative capacity of cells grown in vitro more than 50 years ago (4). Since this seminal discovery, the field of senescence has grown, with many ongoing efforts investigating its role in development, homeostasis, aging, and cancer.

However, studying senescence in living organisms has been challenging due to the difficulty in identifying and characterizing senescent cells in tissues and organs; as yet, a gold-standard biomarker of the senescent state (in cancer cells) remains to be defined.

We have, however, started to learn much from modeling studies. For example, experiments using the INK-ATTAC transgenic mouse model, generated by the van Deursen group, demonstrated how organism-wide elimination of senescent cells can extend the healthy life span and reduce the impact of age-related disorders, such as lordokyphosis and cataracts (5). Demaria and colleagues generated the p163MR mouse, with which they confirmed the positive role of senescent cells in wound repair but the negative effects in senescence.
of chemotherapy-induced senescence in normal tissues (6). More recently, the Bernards group demonstrated the power of a one–two punch method to induce and selectively eliminate senescent cancer cells (senolysis) in hard-to-treat hepato-cellular cancer (7).

These studies provide important insight about the therapeutic potential of perturbing senescence, but we need to understand more to realize this potential. A key element of this Cancer Grand Challenge is establishing reliable biomarkers to identify senescent cancer cells to begin to answer important questions about senescence. The challenge also seeks to understand the physiologic impact of inducing senescence and/or removing senescent cells in the wider context of tumor development, and to identify ways to selectively kill senescent cancer cells.

**E-CIGARETTES**

Despite the increased use of electronic cigarettes (e-cigarettes) over the past decade, including among children and young adults, we do not fully understand the health consequences of their use and whether they are effective at helping adult smokers to quit.

The strength of the evidence regarding e-cigarettes as a tool to aid smoking cessation is currently assessed as very low to moderate, according to systematic reviews employing GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria for assessing certainty of the evidence. This is attributed to the limited number of randomized trials, heterogeneity across studies, methodologic and sampling limitations, and imprecision of results—both statistically and due to a small number of relevant studies. Moreover, few studies account for important variables related to characteristics of e-cigarette products used (e.g., nicotine content, voltage settings) and patterns of use (e.g., frequency, intensity; refs. 8, 9).

Furthermore, the evidence is still emerging regarding the short- and long-term health harms of e-cigarette use and how these products affect tobacco use patterns, including initiation, dual use of e-cigarettes and cigarettes, and smoking cessation (10). Toxicant levels are generally lower in e-cigarette aerosol than in cigarette smoke. Although the current body of research remains limited, research in cell systems, animal models, and humans demonstrates that e-cigarettes and their associated chemicals can have adverse effects on multiple organ systems, including the cardiovascular, respiratory, and immune systems (11). Moreover, youth e-cigarette use presents increased risk of health harms, including nicotine addiction, harm to the developing brain, and increased risk of cigarette smoking (10, 12).

Carefully designed and rigorous studies are needed to determine the harms of e-cigarette use and any potential benefits. Multinational and multidisciplinary approaches are essential given the proliferation of e-cigarette products and various country-specific regulatory strategies, which can present challenges for synthesis across individual studies. This Cancer Grand Challenge aims to generate objective, high-quality studies to inform the general public, including adult smokers who may consider using the products to quit smoking, clinicians, and public health authorities.

**NORMAL PHENOTYPES**

In 1975, Mintz and Illmensee reported establishing a normal, fertile mouse from a malignant teratocarcinoma line, providing compelling evidence that cancer cells could adopt a normal phenotype (13). More recent studies have demonstrated how sun-exposed skin contains a patchwork of evolving clones, with more than a quarter of the cells containing cancer-associated mutations; yet, despite this, sun-exposed skin maintains the physiologic functions of normal epidermis (14). This discovery was paradigm shifting, challenging the assumption that cancer driver mutations occurred rarely in long-lived cells and that most existed in malignant tissues too small to be detected in the clinic. Multiple studies from a number of different groups have since corroborated the findings in other tissues, including esophagus, lung, liver, and breast.

We have also known for some time that cancer is associated with the disruption of normal tissue architecture, breakdown of tissue boundaries, stromal changes, and angiogenesis. Early studies demonstrated an integral role for the extracellular matrix (ECM) and stromal microenvironment, including importance of the tensile strength, mechanochemical regulation, in carcinogenesis (15). In addition, early insights from the Cancer Grand Challenges Mutographs team (supported in an earlier round of the initiative) are starting to revive the promotor hypothesis, which posits that processes such as wound healing and inflammation may act to promote malignancy in cells harboring oncogenic mutations (16).

With this Cancer Grand Challenge, we ask teams to consider what we now know about mutational load in normal cells, combined with cell-extrinsic factors such as the role of the ECM, tissue architecture, metabolite availability, inflammation, and the potential role of systemic responses (e.g., the immune system), to uncover the underlying mechanisms that allow these cells to be phenotypically “normal,” and the necessary molecular events that drive them to malignancy.

**INFLAMMATION**

We know there are many environmental and lifestyle factors that increase an individual’s risk of cancer, but for many risk factors the biological mechanisms by which they lead to cancer development remain elusive. Inflammation is a major biological process that often ensues with exposure to carcinogens, yet we know relatively little about the cellular and molecular mechanisms linking inflammation and carcinogenesis.

The link between inflammation and cancer is likely to be vast and complicated. Dvorak described tumors as wounds that never heal (17), with more recent studies linking the pathology of some tumors with inflammatory processes that occur as a result of normal wound healing (18). In 1941, Rous and Kidd suggested that tumors arose from an initiation state, where cells containing mutations remain normal until a secondary event, such as inflammation, occurs to promote growth of these cells—linking this challenge intimately with elements of the “Normal Phenotype” challenge concept (19) described above.

Many unanswered questions remain about the array of events that can stimulate tumor-enhancing inflammation. How many “types” of inflammation are there and do they each have similar effects on tumor development? What is the
effect of inhibiting inflammation at different stages of tumor development? How does age affect the quality and potency of the immune response?

Through this Cancer Grand Challenge, we hope that teams will examine the causal mechanisms linking inflammation and cancer initiation, to provide opportunities for cancer prevention and important markers for diagnosing early-stage cancer.

**SOLID TUMORS IN CHILDREN**

With the introduction of chemotherapy in the 1960s and the use of combination approaches, survival from some pediatric cancers has increased dramatically. This is particularly true for pediatric hematologic cancers. Genomic profiling revolutionized our understanding of the genetic basis of acute lymphoblastic leukemia (ALL), and the use of tyrosine kinase inhibitors with chemotherapy in BCR-ABL-positive ALL is an excellent example of targeted therapy, yielding a 3-year event-free survival of 80%, more than twice that of historical controls (20). Considerable efforts have also led to the development of chimeric antigen receptor (CAR) T-cell therapy for use in pre-B-cell ALL by targeting CD19 (21). CAR T-cell therapy was FDA-approved for B-cell malignancies in 2017, and its application continues to expand, particularly for hematologic malignancies.

In general, however, the progress made in pediatric hematologic cancers has not been mirrored in solid tumors—with survival rates for some tumor types remaining depressingly low. There are a multitude of reasons behind this lack of progress. First, many of these tumors are rare, making building research programs difficult. A further critical issue is a lack of effective therapies for pediatric solid tumors, because many new therapies are developed to exploit vulnerabilities present in adult but not pediatric cancers. For treatments that do show efficacy, many result in serious long-term morbidities and associated health complications, including learning difficulties, abnormal growth, and infertility. An additional challenge for brain and central nervous system tumors is the low permeability of the blood–brain barrier.

We know that many pediatric solid tumors are distinct from adult cancers with respect to their biology and how they respond to therapy. We also know that many of these tumors mimic or hijack developmental processes or derive from cells present during development. A deeper understanding of these features is important if we are to make real progress for pediatric patients. Translating the success of immunotherapies in adult cancers to pediatric solid tumors could be another important opportunity to explore. A global collaborative approach is needed to tackle this Cancer Grand Challenge, advance our understanding of pediatric solid tumors, and translate what we learn into real clinical benefit.

**MACROMOLECULES**

Macromolecules hold considerable promise as effective therapeutics, not just to treat cancer but for many other diseases. Their structure offers high specificity and potency, and, in comparison with small molecules, often they have lower nonspecific binding, less toxicity, and reduced drug–drug interactions.

Yet, their potential efficacy is compromised; many barriers limit the systemic delivery of macromolecules. Their rapid clearance from the blood hampers biodistribution, and we lack an efficient, safe, and specific delivery mechanism. Further reducing their therapeutic potential are phagocytic clearance, their large molecular weight affecting biodistribution, their chemical stability, challenges with their solubility, and, critically, their failure to permeate cell membranes.

Efforts are ongoing to overcome these barriers, with a major focus on nanotechnology-based delivery systems, including efforts to exploit receptors on the blood–brain barrier. Recently, the use of extracellular vesicles (EV) to deliver cargo such as RNAi, CRISPR/Cas9, and chemotherapeutics to target tissues has shown promise, although efficient EV loading, tissue targeting, and the functional delivery of the therapeutic agents must be further explored (22).

Despite significant advances in the field of macromolecule delivery, an ongoing obstacle remains their inability to cross the cell membrane to enter the cytoplasm and nucleoplasm where target molecules reside. Many molecules that bind to the cell surface enter endosomes but cannot escape that membrane compartment.

With this Cancer Grand Challenge, we invite scientists to develop approaches to overcome this barrier, to achieve the noninvasive, systemic delivery of macromolecules, and to create new ways to treat cancer.

**CACHEXIA**

Cachexia is a wasting syndrome frequently associated with cancer and other chronic diseases where sufferers lose weight and experience decline of their overall health. Clinically, cancer cachexia involves dysfunction of multiple tissues and organ systems, drastically decreasing a patient’s quality of life and their tolerance to therapeutics, and is a significant determinant in patient survival.

Despite cachexia having such significant clinical implications, we still know relatively little about the condition. Clinical studies have revealed it is not simply a result of nutritional deficiency, as nutritional supplements do not reverse cachexia in patients with cancer. In addition, although there are numerous clinical trials of agents targeting mediators of cachexia, there are no effective therapies.

We are, however, starting to learn more about its biology, recognizing that although muscular atrophy is the major manifestation of the condition, cachexia is a systemic paraneoplastic phenomenon, affecting or influenced by multiple tissues. Furthermore, recent advances have revealed more about muscle atrophy/hypertrophy and adipocyte wasting/browning (23), and the involvement of metabolism and the immune, endocrine, and central nervous systems in cachexia (24).

To develop effective treatment strategies, we need to fully understand the basic mechanisms that underpin this multifactorial condition. This Cancer Grand Challenge invites teams to build on recent advances and provide a platform for the development of therapeutic approaches to reverse this
debilitating condition, which would significantly improve the lives of patients with cachexia.

DORMANCY

The issue of dormancy and recurrence following seemingly effective treatment remains a significant problem in cancer. Some cancers, for example certain types of breast cancer, undergo a period of dormancy, ranging from years to decades, before metastatic disease recurs.

Observations by Willis (1934) and Hadfield (1954) laid the foundations for the field of dormancy, with Willis noting late metastases in patients without postmortem evidence of local recurrence, and Hadfield proposing that recurrence occurs because dormant cancer cells enter a state of temporary mitotic arrest. For decades, metastasis was thought to occur at the end of a process that led to lethal cancer; in 2003, Schmidt-Kittler and colleagues demonstrated that breast cancer cells could disseminate with fewer genomic alterations than previously thought, lying dormant for many years before acquiring the genomic abnormalities that make them metastatic (25).

Elucidating the mechanisms governing dormancy has been challenging for many reasons. Dormancy comprises a number of different states, dependent on the cell type, cell context, oncogenic signaling, availability of nutrients, oxygen levels, growth factors, the ECM, and systemic responses (26). There may, then, be many different ways to induce dormancy, and this is regulated by active mechanisms. Another important barrier to overcome is the development of reliable model systems to study dormancy; mouse or culture models, for example, may not accurately recapitulate recurrence after several decades, as seen in patients.

Insight into the dynamic cross-talk between cancer and the host is of critical importance to uncover the mechanisms that establish long-term dormancy after seemingly successful treatment and the mechanisms involved in dormant cell reawakening. This Cancer Grand Challenge seeks to develop and apply innovative approaches to accurately study dormant tumor cells, which could change the way we think about cancer progression. The ability to eliminate dormant tumor cells or prevent their reactivation would have huge therapeutic potential to limit the rates of cancer recurrence.

CONCLUSION

Making progress in these fields and attempting to solve these challenges, we believe, demands a new approach. We are seeking to harness ideas from diverse scientific disciplines and the broadest range of experts; with this round of challenges, up to four global, multidisciplinary teams will each receive up to £20m (~$25m) to come together, think differently, and strive for breakthroughs.

From now until April 22, 2021, we invite you to assemble your Cancer Grand Challenges team and submit applications (https://cancergrandchallenges.org/researchers) with the potential to unlock new thinking in pursuit of some of the most complex challenges in cancer research.

Authors’ Disclosures

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