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Voices

The next big questions in cancer research

Our understanding of tumorigenesis and cancer progression as well as clinical therapies for different cancer types have evolved dramatically in recent years. However, even with this progress, there are big challenges for scientists and oncologists to tackle, ranging from unpacking the molecular and cellular mechanisms involved to therapeutics and biomarker development to quality of life in the aftermath of therapy. In this article, we asked researchers to comment on the questions that they think are important to address in the coming years.

Sherene Loi
Peter MacCallum Cancer Centre, Australia

Sex, the dimorphic immune response, and survivorship

Working in a field of a predominately female cancer, breast cancer, results in seeing efficacy and adverse events from a single-sex viewpoint. Lately PD-1/PD-L1 immune checkpoint inhibitors have been incorporated into the routine treatment of early-stage, triple-negative breast cancer patients. We have recently reported that immune checkpoint inhibitors result in reduced oocyte reserves due to ovarian inflammation in mouse models. If this finding is validated in humans, the implications for women of childbearing age are immense, potentially leading to premature menopause and infertility. It is astonishing to realize that very little research has been done to investigate the long-term reproductive or fertility consequences of new agents we investigate in the phase III setting and then prescribe routinely in the curative setting.

While there has been some research, differences in immune related adverse events as well as the immune response between the sexes remains to be fully elucidated and could also be histology specific. The molecular mechanisms underlying this are far from understood even though sex disparities in cancer incidence, prognosis, and treatment responses have long been known to exist. Hence, future trials and biomarker work should also consider including collection of data concerning sex-specific short- and long-term effects of all new agents, especially immune checkpoint inhibitors. As the number of survivors continues to rise as a result of immune targeting agents, these issues become increasingly important.

Jeffrey Settleman
Pfizer Inc., USA

Knocking down tumors—roots and all

The precision oncology paradigm has delivered many cancer drugs over the past two decades. However, the limited number of additional opportunities associated with relatively common mutations suggests that the "low hanging fruit" has been largely plucked, and we are reaching a point of diminishing returns. This treatment paradigm is further challenged by the nearly inevitable emergence of drug resistance due to underlying intratumoral heterogeneity. While many rationally targeted treatments can effectively "prune the branches of the tumor tree," they generally fail to "pull out the roots"—the cancer cell subpopulations whose viability appears to be independent of those signaling pathways that drive proliferation of the "bulk" tumor cell population. Such cells likely limit the potential to produce curative outcomes in patients with advanced cancers. With emerging technologies, including single-cell genomics and live-cell imaging, there is an important opportunity to elucidate mechanisms underlying the dynamic plasticity of tumor cell populations as a key step toward the discovery of novel treatment strategies that exploit vulnerabilities within individual cancer cells that are not readily revealed through bulk tumor analysis. Moreover, a deeper understanding of the role of epigenetic regulation in establishing intratumoral heterogeneity will also be required to effectively disrupt the phenotypically distinct co-existing cellular states that constitute a single tumor. Such advances will ultimately be needed to produce durable remissions and possibly cures for patients with lethal malignancies.

Johanna A. Joyce
University of Lausanne, Ludwig Institute for Cancer Research, Switzerland

Therapeutically targeting tumor ecosystems

How can we unravel and therapeutically target the immense complexity and diversity of the tumor microenvironment (TME)? This is one of the big questions to address in cancer, and thanks to critical advances in recent years, we are much closer to achieving this goal. Pan-cancer studies, incorporating single-cell analyses and spatial transcriptomics, have revealed intricate cellular ecosystems connecting different cell types in the TME and defined spatial niches, which can serve as cellular hubs for crosstalk between cancer cells and the vasculature, immune, and stromal cells. Over the coming years, we will therefore need to move beyond the current focus on investigating individual cell types of interest to embrace a comprehensive systems-level approach in which we integrate all TME components as a strategy to identify and target these critical hubs. We also now recognize that the TME is a key driver of multiple, potent immune suppressive mechanisms. Thus, one example of where we can expect major advances will be in the targeting of the TME in combination with immunotherapies—to unleash the full power of the adaptive immune system against cancer. Integration of the patient as a whole will also be critical—to unravel how systemic conditions, including obesity, cachexia, inflammation, and aging, can impact the TME and therapeutic outcome. Looking forward to the next decade, I am very optimistic that we will achieve the long-held potential of effectively targeting the TME for the benefit of many more cancer patients.

C.S. Pramesh
Tata Memorial Hospital, Tata Memorial Centre, India

"Earthshots over moonshots" in cancer research

Today, more than ever before, there is an urgent need for research that is globally relevant rather than limited to regions with high Human Development Index. With much of the cancer burden likely to fall on low- and middle-income countries (LMICs), it seems incongruous that almost 90% of cancer research currently takes place in high-income countries (HICs). Neither the discordance between the cancer burden and research funding in HICs nor the types of problems or solutions addressed in these countries are relevant to the majority of patients with cancer in the world.

When a group of us with global experience in cancer control brainstormed on what global research priorities should be, we identified five broad thematic areas (the cancer "earthshot") that were especially relevant: reduce the burden of patients presenting with advanced disease; improve access, affordability, and outcomes in cancer care via solution-oriented research; country-level health economic assessment of cancer interventions and technologies; quality improvement and implementation research; and leverage technology supported by robust data to improve cancer control. These are not problems currently prioritized by HICs or industry. Yet, these are the critical issues in cancer facing most of the world's population. Now is the time for the global community to wake up, take notice, and change the direction of cancer research for the larger public good.

Rene Bernards
The Netherlands Cancer Institute, Netherlands

It's combinations, stupid

Resistance to therapy remains a major obstacle in the treatment of cancer. The AIDS pandemic has taught us that use of multiple drugs having non-overlapping resistance mechanisms can make a deadly disease with high mutation rate chronic. Making cancer a chronic disease is therefore simple in principle—develop highly effective combination therapies. A practical problem is that there are well over 1,000 cancer drugs either approved or in development, allowing for near endless combinations.

In spite of the fact that there are already drugs available for nearly every cancer-relevant pathway, there remains a major emphasis on the development of drugs against novel targets in oncology. Unsurprisingly, these new drugs run into the same problem of resistance development as their predecessors. This focus on additional drugs is driven, at least in part, by the need of the pharmaceutic industry for patent-protected drugs that can be sold at a premium over generic drugs.

In recent years, technologies have become available to identify powerful synthetic, lethal drug combinations whose activity far exceeds that of the individual single-agent

therapies. Such rational drug combinations can help delay resistance development in advanced cancers and hold the promise to be curative in earlier-stage cancers. I believe that academic researchers can deliver more clinical benefit to patients by focusing on finding highly effective combinations of existing drugs than by searching for more drug targets. Over time, this would also contribute to affordable healthcare through use of more generic drugs.

Jia Fan
Zhongshan Hospital, Fudan University, China

Boosting neoantigen-specific immune response

Immunotherapy, including checkpoint inhibitors, is promising for cancer treatment, but only a minority of patients respond. The mechanisms for resistance to immunotherapy are multifaceted and highly personalized, such as T cell exclusion, lack of tumor immunogenicity, and disruption of antigen presentation. Additionally, each patient's demographic, psychophysiological, and (epi)genetic backgrounds, as well as prior treatments, will generate a unique antigen and therapeutic landscape.

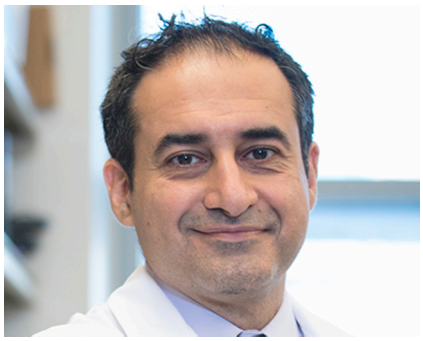
Exploiting the inherent nonself properties of cancer cells to enhance cancer-specific immunity may aid in overcoming resistance. Neoantigens, derived from but not limited to cancer intrinsic alterations like SNV, Indels, fusions, and splicing variants, serve as the most promising targets to generate anticancer responses. Neoantigen vaccination (e.g., mRNA or peptide delivery) and engineered T cell transfusions (e.g., $KRAS^{G12D}$ TCR-T) can stimulate and expand neoantigen-specific T cells, ultimately leading to recognizing and killing neoantigen-presenting cancer cells. Again, the overall response may be boosted by combining with appropriate immunostimulatory or non-immune strategies (e.g., radiotherapy, chemotherapy, or oncolytic virotherapy) to induce immunogenic cell death and neo-epitope spread as an *in situ* vaccine.

These neoantigen-directed immunotherapies are intended to exert more specific immune selection pressure, achieving extensive and sustainable responses for diverse individuals. Clinical trials of neoantigen-directed therapy plus immunosensitization approaches will be necessary to confirm their efficacy and determine the specific contribution of these immune interventions.

Juanita L. Merchant
University of Arizona, USA

Biomarkers, precursors, and biospecimens

I see three major questions for cancer research. First, biomarkers and drug targets may be the same molecule or within the same pathway, but biomarkers do not carry the same concerns about toxicity and off-target effects. Thus, biomarkers theoretically are more likely to be implemented into clinical practice before new therapies. That being said, the sensitivity and specificity of the biomarker(s) are critical. Although sensitivity and specificity are highly desired, but rarely achieved, I would caution that biomarker utility will garner higher interest if highly specific. Second, apply the biomarker concept to the identification and monitoring of precursor lesions. In both gastric and esophageal cancer, metaplastic cells are the pre-neoplastic cell population indicating that chronic insults to the organ (typically inflammation) have initiated transformation. However, since it is unclear when actual cancer will emerge, patients worry about this pre-diagnosis, while clinicians spend extensive time and limited resources monitoring these lesions. Like these gastrointestinal cancers, there are other pre-cancer states that are recognized, but do not have widely available biomarkers to assess when to screen patients and how often. Third, racially and ethnically diverse biospecimen collection from human participants will be essential to discover, characterize, and implement useful clinical biomarkers. To that end, more efforts are needed to train more researchers in a range of disciplines from epidemiology to cancer biology to clinical trials.



Javid Moslehi
University of California San Francisco, USA

Cardio-oncology: A platform for physician-scientists

Following the completion of a cardiology fellowship, I started a research fellowship at the Dana-Farber Cancer Institute where I realized that many novel cancer therapies were leading to cardiovascular adverse effects, both during treatment and survivorship. Cardio-oncology is a progressing frontier that extends beyond drug toxicity. For example, patients with clonal hematopoiesis of indeterminate potential are at risk for both cardiovascular disease and cancer. With a robust clinical program in place, we are entering unchartered waters. For instance, patients treated with immune checkpoint inhibitors can have fulminant myocarditis. To begin to understand these connections, we have created preclinical models that show a previously unappreciated role for immune checkpoints in the heart. The use of abatacept (CTLA4-Ig) rescues the mouse phenotype, with our early clinical data suggesting an effective treatment strategy for myocarditis. Because of the targeted nature of new cancer therapies, cardiovascular sequelae may provide insights into cardiac biology, making cardio-oncology a novel platform for cardiovascular investigation. We aim to train the next generation of leaders in the field to bring diversity in background and thought and strong intellect to the challenge of improving patients' lives through innovation in research, clinical care, and education.

William R. Sellers
the Broad Institute of MIT and Harvard, and the Dana-Farber Cancer Institute, USA

Rare cancers

Rare cancers are only rare in isolation. Estimates place the burden of rare cancers at 20%–24% of all cancer diagnoses. We make great strides in targeting subpopulations of common cancers that are rare (e.g., neurotrophic tyrosine kinase receptor [NTRK] fusions) or even specific mutation subsets within known oncogenes. Yet, we struggle with developing therapeutics and even more so with making therapeutic insights in rare cancers. Why? First, access to patients, patient samples, and patient outcome data is fragmented across geographies and medical centers, leading to isolated case reports rather than a well-defined understanding of the clinical disease and the response to therapy. This is further exacerbated by disease-oriented cancer care, which can dilute the rare cancer population. Second, the nature of the fragmented ecosystem leads to great difficulty in conducting timely and robust clinical testing of new therapeutics in rare cancers including those that might already exist for other cancers. Finally, the preclinical study of rare cancers is severely limited by the lack of appropriate cancer cell lines, organoids, or primary derived xenograft models, making it exceedingly challenging to discover new targets or validate therapeutic hypotheses.

Unfortunately, funding for rare cancer research is limited. Yet, investments here could come with marked patient benefit—many rare cancers have relatively simple genomes, meaning new therapeutics might have significant long-lasting impact. New initiatives supporting direct-to-patient cohort enrollment bridging geographic fragmentation and rare cancer model development, enabling preclinical research to accelerate, are the first steps along a path toward curing these diseases.

DECLARATION OF INTERESTS

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