Directions to overcome therapy resistance in cancer

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Novel modalities for treatment of cancer have emerged because of advances in technology that have enabled expansion of our understanding of how cells transform to become cancerous and the role of the tumor microenvironment (TME). However, resistance to therapy poses a major problem for the successful treatment of cancer. Ongoing collaborative efforts of clinicians and researchers from different parts of the world have also led to an emerging understanding of how cancer cells evolve to resist treatment. Jerry Madukwe, the Editor-in-Chief of *Trends in Pharmacological Sciences* asked experts in the field to reflect on the global challenges in the cancer field and provide their views on what they see as the most pressing questions and research directions to overcome therapy resistance in cancer.

Advances in single cell technologies provide great opportunities for understanding drug resistance mechanisms


Ruth Nussinov

Ruth Nussinov: Creating guidelines to overcome therapy resistance in cancer is the ultra-challenge. There is much we still do not know. One glaring example involves RAS. Despite the huge focus over the past decade on RAS and its mutations and the NCI RAS initiative, only recently was it discovered that KRAS resistance mutations in highly aggressive pancreatic ductal adenocarcinoma (PDAC) can couple with Myc copy number increase. We ask: are there additional KRAS-related overexpression resistance mechanisms in PDAC? Over- (under-) expression is an acquired aggressive mechanism. It is also observed in, for example: the aggressive HER2 overexpression (of EGFR) in breast cancer; and ALK rearrangements, ROS1 rearrangements, MET, and RET in lung cancer. Overexpression appears to be a hallmark of the most aggressive cancers; yet, the compendium of its combinatorial targets and mechanisms remains elusive.

Developments in single cell sequencing, transcriptomics, and, recently, spatial biology over time, can help. They can identify alterations in cell trajectories associated with cell differentiation, and probe therapy response in distinct cell populations. However, no clear way has been outlined for exactly how to harness these approaches to overcome the ultra-challenge of drug resistance.

Despite exciting drug innovations, such as the KRASG12C covalent drugs, which showed that drugging the undruggable is possible, resistance remains unresolved. We still struggle with detecting rare pre-existing (intrinsic) mutations in tumor subclones and are still unable to conceive guidelines to overexpression scenarios, emphasizing that more data and new conceptual advances are essential.

Tumor heterogeneity correlates with cancer aggressiveness and resistance. Heterogeneity increases during cancer evolution, with the emergence of additional mutations, gains in gene copy number, fusion of transcription factors, epigenetics modulation, and more. Better understanding of the mechanisms will help guide future cancer treatments and achieve better outcomes. Drug resistance mutations, either existing before treatment, or emerging during/after therapy (acquired), are responsible for cancer recurrences.

I believe that identification of all possible alternative (parallel, redundant) pathways, compensatory pathways, and, importantly, crosslinks, ideally tagged with cell-specific data, are the vital gaps that future research should address, given that overexpression and activation mutations corrupt and activate multiple oncogenic pathways.

Metabolic vulnerabilities of the tumor microenvironment


Thomas Weichhart

Thomas Weichhart: Many metabolic traits previously identified in tumor cells *in vitro* are not well preserved *in vivo* or are now understood to be features of the TME. For instance, the Warburg effect, while a classic observation, is not seen in many patients with cancer and the increased uptake of glucose tracers detected by positron emission tomography is in fact a feature of tumor-associated macrophages. The TME, comprising various immune and stromal cells, is now recognized as a pivotal determinant of tumor progression and response to anticancer therapies.

Traditionally, large compound libraries have been screened against cancer cells, but they could also unveil compounds targeting or eliminating tumor-promoting immune cells. Such screenings might reveal specific cellular and metabolic vulnerabilities in tumor-associated macrophages or regulatory T cells, enabling their selective depletion while preserving beneficial immune subtypes. Moreover, immune-directed therapies should consider the recently identified immune subtypes present in various cancers, because immune cell diversity within the TME will directly influence the success of, and resistance, to anticancer treatments.

Although immunotherapies targeting the TME have shown success, a significant portion of patients do not respond, underscoring our incomplete understanding of the intricate interplay between the TME and tumor cells. Immune cells within the TME may exhibit less metabolic flexibility compared with tumor cells, making them attractive therapeutic targets.

Integrating AI and holistic approaches to combat cancer therapy resistance globally


Zodwa Dlamini

Zodwa Dlamini: Artificial intelligence (AI) holds immense potential in revolutionizing cancer care by enabling more accurate and efficient diagnoses, personalized treatment planning, real-time monitoring of patient response, and even drug discovery. AI-driven algorithms can sift through vast data sets to identify potential drug candidates, predict their efficacy, and optimize treatment regimens. By harnessing the power of AI-driven technologies, we can enhance the precision and efficacy of cancer therapies while minimizing adverse effects, thereby improving overall patient outcomes. I firmly believe that interdisciplinary approaches, coupled with the integration of cutting-edge technologies, such as AI, offer promising avenues for surmounting therapy resistance in cancer, particularly in low–middle income countries, where resources for cancer research and treatment may be limited.

Looking toward the horizon of cancer research, we now have a pivotal opportunity for fostering innovation and collaboration on a global scale. Elucidating the intricate mechanisms underlying therapy resistance, identifying robust biomarkers for facilitating personalized treatment strategies, and leveraging AI-driven drug development to expedite the discovery of novel therapeutics are critical gaps to address. Based on my experiences in the field and also leading a Pan African Cancer Research Institute, to address these gaps head-on, it is paramount to cultivate an innovative and collaborative scientific community that transcends geographical boundaries and disciplines. These guiding principles serve as the cornerstone for addressing therapy resistance and steering the trajectory of cancer therapy development toward a future characterized by improved outcomes and heightened resilience.

The spectrum of perspectives regarding cancer therapies encompasses an array of modalities, from traditional methods to the forefront of scientific advancements, such as immunotherapy and precision medicine. Embracing this diversity of viewpoints, I advocate for the adoption of a holistic approach that synthesizes the strengths of various treatment modalities to achieve optimal patient outcomes.

The field needs to couple strong mechanistic and translational science to gain a greater understanding of the underlying tumor and immune biology


Don L. Gibbons

Don L. Gibbons: The thinking in oncology and our therapeutic approaches over the past two decades have been transformed by a shift away from focusing solely on tumor cells and toward systems-level and whole organism-level biology. The application of, and clinical successes with, immune checkpoint blockade (ICB) therapies are paradigmatic of this progress. Unfortunately, most patients still do not derive durable benefits from current immune therapies.

I came into thoracic oncology during my medical training because it is a field with significant clinical need for new therapies and where I could apply my prior training in biochemistry and cell biology. My group has been interested in understanding the interactions of tumor cells and their microenvironment that drive cancer progression, metastasis, and response or resistance to targeted or immune-based therapies. Technologies, such as single cell transcriptomics and spatial analyses, are helping to define the heterogeneity of tumors and the interaction of the various components, including tumor cells, extracellular matrix, and other heterotypic cell types, such as the various immune cell types. However, these tumor and host complexities also present significant challenges for the selection and application of immune-based treatments to individual patients, especially given the dynamic nature of tumors over time and in response to treatments.

The field needs to couple strong mechanistic and translational science to gain a greater understanding of the underlying tumor and immune biology with the development of therapeutics for specifically selected patient subsets, where patient selection has become significantly more involved compared with DNA sequencing of the tumor. The roles of the TME, the immunogenicity of the tumor, the overall patient immune status, gut and tumor microbiome, along with meaningful clinical assays for these factors, will need to be refined and integrated into clinical decision-making.

Deciphering the molecular and cellular mechanisms underlying cancers


Isabelle Van Seuningen

Isabelle Van Seuningen: Development of targeted therapies and immunotherapies has recently allowed better care of patients with cancer. Despite these advances, incidence and mortality by cancer are still increasing and cancer remains a public health issue worldwide. Moreover, resistance to these new therapies represents an even bigger challenge.

Over the past few decades, cancer research has evolved from studying the tumor itself to considering the role of the tumor and its microenvironment. Technological advancements, such as single cell analysis, AI for identifying early lesions, spatial transcriptomics, and proteomics have provided scientists with tools that allow precise definition of the heterogeneity and plasticity (stemness, epigenetics) of tumors, specific to each patient and that guide optimal treatment selection. In my role as the director of the Cancer Heterogeneity, Plasticity and Resistance to Therapies (CANTHER) laboratory, and the ONCOLille Interdisciplinary Cancer Research Institute in Lille, France, we continue to decipher the molecular and cellular mechanisms underlying cancers to enable discovery of new molecules and/or new combinations to better treat the patients. In my own research, I have switched from studying the role of secreted mucins in hypersecretory pathologies in the respiratory and gastrointestinal tracts to studying the role of mucins in cancers. The MUC4 transmembrane mucin, which was discovered in my laboratory, forms an oncogenic complex with ErbB2 at the surface of epithelial cancer cells. We are now aiming to

develop therapeutic inhibitory small molecules that target ErbB2-MUC4 complex to overcome ErbB2/HER2 therapeutic failure in cancers.

Another priority is to detect cancer early, aided by the development of new biomarkers, to greatly reduce the heavy costs of treating late-stage cancers. It is also important that societies work on initiatives to promote cancer prevention and the onset of cancer, and on early diagnosis to not only allow earlier intervention before a tumor metastasizes, but also work on patient quality of life during and after treatment and when returning to daily life.

Personalized immuno-oncology


Jessica Konen

Jessica Konen: While immune checkpoint inhibitors have undoubtedly changed the clinical management of cancer, the full success of these agents has been hindered largely due to resistance. However, I am particularly excited by the rapid expansion of this field as a result of significant advances in sequencing and spatial technologies over the past decade, particularly at the single cell level. These technologies unlock ample opportunities to learn about tumor evolution in the face immunotherapy with increased granularity, not only creating novel opportunities to target specific vulnerabilities, but also providing data sets for generating complex resistance biomarker signatures. My laboratory utilizes these cutting-edge technologies to probe novel mechanisms of resistance. Specifically, we study the pleiotropic effects of immunosuppressive metabolites that diminish response to checkpoint inhibitors. This burgeoning field focused on noncellular factors in the TME influencing antitumor immunity presents vast opportunities for improving cancer immunotherapy response.

Despite these advances, there are numerous challenges that must be tackled to pave the way for personalized immuno-oncology. For example, the line between the biological and computational/data sciences has blurred with the increased need for large data mining and the integration of machine learning in biomarker development and response prediction. To

address this, we need to create new mechanisms to encourage interdisciplinary collaborations. An additional challenge is the reliance on inadequate mouse models, which limits progress, especially considering the vast differences in the immune system between mice and humans, and other important host-related factors. Increased utilization of models better recapitulating human disease, such as patient-derived organoids, as my group has begun to test, is necessary for improving the likelihood of clinical success for new therapeutic strategies. By coming together as a global scientific community to address these and other challenges, we can make significant strides toward more efficacious cancer therapeutics to improve patient outcomes.

The need to identify novel immunotherapeutic targets


Huai-Qiang Ju

Huai-Qiang Ju: The breakthrough success of immunotherapy, particularly ICB, has revolutionized cancer treatment. Despite this, only a small subset of patients with gastrointestinal cancer respond to ICB, indicating the imperative need for a deeper understanding of the underlying molecular mechanisms and the development of targeted interventions. My research mainly focuses on investigating the regulatory mechanisms of metabolic and immune interactions in the gastrointestinal TME (e.g., colorectal cancer), with the aim of identifying effective intervention strategies. The heterogeneous nature of the TME has a major role in impairing immune responses and fostering resistance to ICB. Recent advancements in spatially and temporally resolved multi-omics single cell analyses offer a comprehensive approach to deciphering the dynamic features of the TME across primary or metastatic gastrointestinal cancer. Identifying novel molecular classifications or immune cell subsets associated with immunotherapy efficacy is essential for strategizing personalized treatment approaches. Moreover, recent studies emphasize the importance of identifying novel immune checkpoints or regulators present in various immune cell types for optimizing cancer immunotherapy. Despite current advancements in this field, there are still gaps in our understanding of the immune regulatory network. Therefore, it is essential to explore new immunotherapeutic targets beyond tumor cells or T cells, extending to include other immune and stromal cells. Mechanistic studies provide a theoretical basis for the

identification of novel immune regulatory molecules. Innovative experimental techniques, such as CRISPR/Cas9-based gain/loss-of-function screening, also provide effective strategies for identifying these molecules. In addition, recent experimental and clinical studies have demonstrated synergistic effects when combining ICB with chemotherapy, dietary interventions, or modulation of the gut microbiota to overcome resistance. Thus, thorough preclinical and clinical investigations into these combination strategies are still needed. Taken together, despite the significant challenges that persist, I am optimistic that these endeavors will lead to substantial progress toward achieving more durable therapeutic control of gastrointestinal cancers.