A roadmap for the next decade in cancer research

Cancer research in recent years has been marked by significant developments in understanding disease biology and foundational discoveries that have changed clinical practice. Ten cancer researchers take stock of the field, the advances that excite them, key outstanding questions and breakthroughs they anticipate looking forward.

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The turn of the decade marks a period of remarkable progress for cancer research. Advances in sequencing technologies and model systems have yielded unprecedented resolution of the molecular, cellular and genomic complexity of cancer. The era of big data has changed how researchers operate in the lab and has accelerated collaboration between basic research and clinical practice, and the field has embraced new connections between diverse research areas.

As we launch *Nature Cancer* and embark on our journey to serve and inspire this community, we reflect on progress made, enduring challenges and the road ahead. We asked ten scientists who approach cancer from diverse perspectives about the key developments in their fields and what they envision will be the next breakthroughs in cancer. Together, they highlight valuable advances across disciplines, from understanding mechanisms and risk factors to improving therapies and clinical care, and emphasize the role of emerging scientific fields and technologies in tackling these complex questions.

René Bernards: identifying novel cancer vulnerabilities

Many of the newly developed cancer drugs target the products of oncogenic drivers—genes that became hyperactive as a result of cancer-causing mutations. With this pool of 'low-hanging fruit' targets nearly exhausted, where do we go next in drug development?

A first new area for drug discovery takes advantage of the notion that even undruggable cancer targets can be targeted indirectly. This approach relies on the concept that a cancer-selective mutation can result in an acquired vulnerability that in turn can be drugged. The best-known and clinically relevant example is the finding that loss of the *BRCA1* or *BRCA2* gene results in an acquired sensitivity to inhibitors of poly(ADP-ribose) polymerase. Similarly, drug–drug synthetic-lethal interactions have been discovered through loss-of-function genetic screens, some of which are nearing clinical application. While such developments are promising, a limitation of synthetic-lethal drug pairs is that some are too toxic to be effective clinically. An approach that avoids this problem of combination toxicity is the development of drug therapies that are given sequentially but still show strong synergy. This 'one-two punch' strategy depends on the induction of a major new vulnerability with a first drug that is subsequently targeted by a second drug. Induction of senescence in cancer cells may be a particularly fruitful way to accomplish this, given the stable nature of the senescence phenotype and the major changes in physiology in senescent cells.

Resistance to (combinations of) cancer drugs has been the biggest hurdle by far in controlling cancer to date and is the result of the inherent heterogeneity found in genetically unstable tumors. When cancer cells become resistant to therapy, there is a fitness cost to pay that could result in new vulnerabilities that can be targeted. This acquired vulnerability of drug-resistant cells is also referred to as 'collateral sensitivity'. As one example, the resistance of *BRAF*-mutant melanoma cells to selective inhibitors of BRAF and MEK is accompanied by an acquired vulnerability to histone-deacetylase inhibitors.

An important insight is that often resistance to therapy is not acquired during therapy but is pre-existing in the tumor. Drug resistance often follows a predictable path, as is, for instance, the case for *EGFR*-mutant lung cancer targeted with selective inhibitors of EGFR. Rather than waiting for such drug-resistant tumor cells to emerge and become a major component of the tumor mass (with associated heterogeneity), it might be worthwhile to study the acquired vulnerabilities of such drug-resistant cells in the laboratory to develop drugs to selectively kill them. Rather than treating the acquired vulnerability after resistance has developed, it would make more sense to deplete these cells upfront with a 'pre-emptive strike'. The remaining tumor cells should be more homogeneous and therefore should respond better to the drug that targets the original vulnerability.

As our understanding of the genetic wiring of cancer cells increases, so will our ability to outsmart cancer cells by finding the spots to hit them where it hurts the most.

Elizabeth Jaffee: immunotherapy comes of age in the era of precision medicine

Immunotherapy is an established pillar of cancer treatment. Few new therapies have engendered as much excitement in such a short time as immune-checkpoint inhibitors (ICIs) and engineered T cells. It took 25 years of basic science discoveries and preclinical and clinical development before the first ICI, ipilimumab (a CTLA-4-blocking monoclonal antibody), was approved by the US Food and Drug Administration (FDA) in 2011 for the treatment of metastatic melanoma. FDA approval of antibodies that target the PD-1–PD-L1 pathway quickly followed 3 years later. Since 2014, ICIs for more than 30 indications have received FDA approval and have provided durable survival rates for many patients with metastatic cancer. FDA approval of chimeric antigen receptor (CAR) T cells showed that

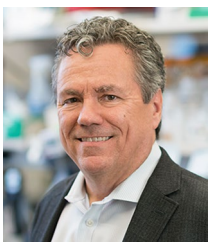
there is more than one form of successful cancer-type-specific immunotherapy that can treat deadly cancers. There are several reasons that immunotherapy has triumphed now, after many decades without clinical progress. First, advances in genomic and proteomic technologies have accelerated the rate at which immune signaling pathways are being elucidated. Second, advances in technologies for engineering humanized and human antibodies accelerated the clinical testing of drugs that modulate specific immunoregulatory signals on T cells. The first clinical testing of antibodies that block these pathways used traditional phase 1 clinical trial designs that evaluate toxicity versus response rates in multiple tumor types regardless of the tumor's genetic and inflammatory composition. However, recent technologies have also accelerated the identification of biomarkers within tumors that can be used to predict response to ICIs. Since the approval of ipilimumab, two biomarkers have been identified that are predictive of responses to current ICIs (tumor mutation burden) and to specific inhibitors of PD-1 and PD-L1 (PD-L1 expression levels on tumor cells). These biomarkers identify specific genetic and inflammatory tumor microenvironments (TMEs) and are now used to identify patients most likely to respond to ICI; thus, toxicities in patients unlikely to respond can be avoided. Also, next-generation sequencing technologies have expedited identification of the specific mutations expressed by a tumor. This has enabled the development of vaccine and genetically engineered T cell strategies that utilize patient-specific mutations to raise the number and quality of mutation-specific T cells in an individual patient. These novel approaches provide cancer-targeted T cells to patients with cancer who are naturally unresponsive to ICIs due to low or no available T cells at baseline. Early clinical trials have shown additional success when patient specific T cell approaches are combined with ICIs that can enhance T cell activity. The future of precision immunotherapy will continue to become patient specific on the basis of both the T cell composition and immune-checkpoint environment within each patient's cancer. Repetitive biopsies at tumor progression should be encouraged to uncover changes in the dynamic TME over time, and to provide the opportunity to rapidly design additional T cell and immune-checkpoint therapeutics to achieve long-term clinical responses in patients whose cancer has become a chronic disease. Further success will also require the development of biomarker-targeted non-invasive imaging and liquid-biopsy tools that can be used to predict early changes in the TME and to allow fine-tuning of patient-specific T cell responses.

Johanna A. Joyce: understanding the TME

Our knowledge of the TME has increased exponentially in recent years, and with this abundance of information, we are now faced with the challenge of unraveling the incredible complexity of the TME. In the early days of TME research, there was perhaps an overly optimistic view that therapeutically targeting normal cells in the TME might represent a 'one size fits all' approach that could be applied to any cancer, regardless of the organ in which it develops. Of course, we now appreciate that while there may be a general set of cell types that constitute the TME (innate and adaptive immune cells, blood and lymphatic vessel networks, stromal cells and the cancer cells themselves), the precise composition, and the contribution of the extracellular matrix, can differ profoundly depending on the organ in which the cancer develops. As one illustrative example, in brain tumors, not only are there tissue-specific cell types that contribute critically to the TME, including astrocytes, microglia, and neurons, but there is also the unique structure of the protective blood–brain barrier, which exquisitely controls the entry of cells and drugs into the brain. Therefore, we cannot simply extrapolate findings from one cancer microenvironment to another.

In addition to important contrasts between organ TMEs, an emerging view in the field is that different genetic drivers can serve distinct roles in sculpting the TME even within the same tissue type, which results in differential effects on the abundance of specific cell types and their 'education' within the TME. Moreover, recent studies have revealed that there are even 'microenvironments within the microenvironment' that demonstrate variance in TME composition, phenotype and function depending on the location within the tumor. Given such complexity and diversity between different TMEs, how can we identify and optimally target the key cell types therapeutically? Numerous studies over the past decade and more have tried to address this question by evaluating a range of targets, including the angiogenic vasculature, fibroblasts and stroma-associated processes, tumor-associated macrophages, etc., with the most successful example thus far being that of immunotherapies that boost the infiltration and/or activity of T cells in the TME. Nonetheless, immune-based therapies are currently effective in only a subset of cancers, and a major mechanism that limits their efficacy is an immunosuppressive microenvironment.

Thus, the path forward will require moving beyond the current emphasis on investigating individual cell types of interest to embrace a comprehensive systems-level approach in which we integrate all TME components as a means of identifying and targeting the critical nodes. We also need to appreciate that the TME is a moving target that changes not only during tumor progression but also following therapeutic intervention. Therefore, dynamic analyses of the TME, such as through intravital imaging or sequential tissue biopsies in conjunction with 'single cell–omics' and sophisticated computational analyses, will need to be incorporated into our experimental toolkits. Finally, we must broaden our analyses to examine the patient as a whole, to understand how systemic conditions, such as obesity, cachexia, inflammation and aging, can affect the TME and treatment response. Looking forward, in building upon this robust foundation of knowledge, it is finally within our sights to achieve the long-held potential of targeting the TME for the benefit of a much broader patient population.



Scott W. Lowe: next-generation mouse cancer models

Traditional genetically engineered mouse models (GEMMs) of cancer have proven invaluable for understanding cancer mechanisms but have had a smaller impact on translational cancer science. Instead, target-validation and drug-assessment studies have relied more on xenograft models produced by the transplantation of human cancer–derived cell lines into immunocompromised mice. Although improvements in the genetic annotation of human tumors and the use of patient-derived xenografts have overcome some of the limitations of xenograft models, they still neglect aspects of the TME that are key determinants of tumor progression and therapy response.

GEMMs provide a physiological alternative, but they are slow, tedious and expensive, often requiring extensive mouse intercrossing for the generation of relevant experimental cohorts of multi-allelic mutant

mice. This makes functional studies slow, but even more challenging are those aimed at target validation, which require additional inducible alleles for suppression of the target in established tumors. Preclinical studies are made tedious by the impossibility of producing synchronized cohorts of tumor-bearing mice. Few academic or industrial teams have the patience or resources to overcome these hurdles.

Still, new technologies are making GEMMs more accessible. Transposon-mediated transgenesis and CRISPR–Cas9-mediated gene editing enable the rapid production of different genetic configurations without time-consuming germline gene-targeting approaches; inducible shRNA transgenes facilitate target validation by uncoupling tumor initiation from tumor maintenance; and models produced directly from multi-allelic embryonic stem cells or ex vivo–engineered organoid systems enable the production of mice that harbor genetically defined tumors without extensive strain intercrossing.

One game-changing approach involves the introduction of cancer-predisposing lesions directly into tissues through the use of somatic engineering. Here, cDNAs or gene-editing constructs are introduced directly into a small number of somatic cells via viral transduction, hydrodynamic transfection (for the liver) or tissue electroporation. Tumors arise focally, surrounded by otherwise normal tissue, and can metastasize to appropriate sites, accurately modeling human tumor initiation and progression. At the same time, such methods dramatically reduce the time and waste associated with the intercrossing of germline strains that harbor various germline alleles. Moreover, tumors can be rapidly produced in mice of different genetic backgrounds, which greatly facilitates the study of how tumor–host interactions influence tumorigenesis.

Somatic tissue engineering has yet other advantages. Cohorts are produced simultaneously, which facilitates various analyses (including drug testing) in a manner that would be inconceivable with traditional strain intercrossing. Also, these systems are highly portable and often require only the distribution of some plasmids and protocols. Compared with conventional approaches, somatic tissue engineering can accelerate cancer modeling by over an order of magnitude and achieves similar reductions in animal numbers and costs.

Of course, no model system is perfect, and the ultimate relevance and utility of any non-human cancer model will depend on the nature of the question being asked. Still, non-germline mouse cancer models provide a disruptive and accessible platform with which to facilitate basic and translational cancer research.

Elaine R. Mardis: genomics-guided cancer precision medicine

The past 20 years of cancer genomics discovery have provided advanced knowledge about the genomic underpinnings of cancer onset and progression. This individualized recipe of genomic and epigenomic phenomena in each patient with cancer weaves together the germline contributions and somatic contributions that fundamentally change the biology of a cell that turns from normal into cancer. Coincident with our technology- and computationally fueled discoveries, the development of advanced therapeutics that target individual cancer drivers and, in the newest approaches, focus the body's own immune system to target and kill cancer cells, has yielded improved outcomes for many patients with cancer. While they are remarkable, these advanced therapies still impact too few lives and often yield to resistance mechanisms that preclude durable responses. These realities evoke the next frontiers that require our attention so we can improve the future impact of precision medicine. First, we must acknowledge that simple gene-mutation-therapy equations lack the sophistication needed to predict therapeutic targets. Cancers acquire numerous genomic alterations that contribute to their biology and, as a consequence, their vulnerability to therapy. These alterations include methylation- and histone-packaging-based epigenetic changes that cannot be 'read out' by DNA sequence alone. Instead, RNA-sequencing assays have revealed numerous aspects of cancer biology that result from combined genomic and epigenomic changes, including elevated pathway activity and the identification of overexpressed drug-targetable proteins. Furthermore, deconvolution of RNA-sequencing data has revealed detailed aspects of the cancer microenvironment, such as the types of infiltrating immune cells and the expression levels of targetable checkpoint proteins. Second, we must begin to incorporate real-world data and evidence alongside advanced genomic profiling of cancers into therapeutic decision-making. This practice will address several deficiencies of clinical trials that provide registration data for regulatory approval of cancer therapies. For example, trials of targeted therapies often require only indicated mutations in specific genes for enrollment into the study, which is overly simplistic. In addition, including real-world data about approved therapies will adjust for the fact that clinical trials often enroll patients with the most-advanced cancer. By including genomic profiling and response data from those patients who receive an approved therapy in the second or third line of treatment, we can adjust for patients who may experience a response that is more or less durable than the response of those in the clinical trial and coincidentally reveal combinations of alterations that allow better prediction of response to therapy. Finally, we must find effective ways of sharing these data among providers of oncology treatment worldwide, in acknowledgement of the fact that that data sharing will advance the collective knowledge and broaden the impact of precision medicine on all patients with cancer. In my experience, this is what patients with cancer and their families want: not only the potential for personal benefit but also to contribute data that may help other patients with cancer; there is little to no concern about data privacy. Certainly, there are benefits to precision cancer medicine, and enhancing our sophistication in predicting a response and its durability will further these benefits for increasing numbers of our patients.

Sean J. Morrison: understanding tumor initiation

The mutations that transform normal cells into cancer cells have now been catalogued for most cancers, and much is known about the mechanisms by which they act. However, most cells that acquire these mutations do not give rise to cancers; instead, they undergo death, senescence or terminal differentiation. Therefore, the mutations themselves are not sufficient; cellular fate is also influenced by epigenetic and metabolic states, as well as by the tissue environment. Much less is known about how these non-genetic mechanisms influence cancer initiation in cell-autonomous ways and non–cell-autonomous ways. For example, the extent to which metabolic and nutritional differences among cells and among people contribute to cancer initiation is particularly poorly understood; however, recent advances in techniques for metabolomics and isotope tracing in vivo will render this one of the most exciting

areas of cancer biology during the next 10 years.

Another transformative recent discovery is that most or all regenerating tissues appear to become more clonal with age and with chronic tissue injury. That is, stem and progenitor cells acquire mutations that confer a competitive advantage over neighboring cells and that lead mutant clones to become over-represented over time. This has been documented in the blood, skin, liver and esophagus. The mutant clones are not yet cancer cells, but they are partway there. The accumulation of mutant clones in regenerating tissues increases the probability that cancers will subsequently develop, although the risk of transformation to cancer varies widely, depending on the mutations in the mutant clones.

The evolution toward clonality has been studied most extensively in the hematopoietic system. Clonal hematopoiesis is commonly observed in people who have been treated with radiation therapy and certain chemotherapies, as well as in patients older than 70 years of age. A critical question is whether the same is true in other regenerating tissues. Do chemotherapy and radiation therapy promote the development of clonality in all regenerating tissues? Or perhaps clonality arises mainly in response to different mutagens in different tissues: UV light for the skin; hepatotoxic agents in the liver; and smoking and alcohol in the esophagus.

What is the effect of increasing clonality on tissue-regenerative capacity, and is there an effect of age on the response to mutagens? There is a geometric increase in the incidence of clonality with age in the hematopoietic system. Are tissues in older people more likely to develop hyper-competitive clones than are tissues in younger people, after exposure to the same mutagen? If this is observed, it will raise fundamental questions about the effect of age on the response to mutagens and the mechanisms that limit the expansion of mutant clones, including mechanisms related to cell competition. One of the most exciting opportunities over the next 10 years will be understanding the effects of mutagenesis on tissue homeostasis and cancer initiation and how this changes with age.

Kornelia Polyak: tackling metastasis

Distant metastasis is considered the pinnacle of tumor evolution because it is responsible for most cancer-associated deaths. Due to the importance of this issue, scientists have forged a quest to identify drivers of metastasis, predictors of which primary tumors will progress and ways to block

this process. Various genes and plasticity of cellular states involving epithelial-to-mesenchymal transition have been both proposed and disputed as key players in the metastatic cascade, which has triggered intense debates in the metastasis-research community. However, since tumorigenesis is a Darwinian evolutionary process, tumor size, cellular heterogeneity for heritable phenotypic features and topologic diversity of the primary TME might be the most accurate predictors and drivers of metastatic progression—a view most metastasis-gene-focused researchers may not embrace. Furthermore, one of the most effective defenses against tumor-cell dissemination and outgrowth is the immune system. Recent data from multiple laboratories, including my own, now bring all these observations together by demonstrating that non–cell-autonomous factors that drive primary tumor growth via modulation of the local microenvironment also maintain intratumor heterogeneity and have systemic effects on the immune system that enable metastatic outgrowth. Therefore, non–cell-autonomous factors (e.g., secreted proteins and exosomes) may indeed be one of the most critical drivers of tumor progression, including metastasis. This of course does not diminish the importance of genetic alterations within tumors but places them in a different light. Genetic alterations and genomic instability fuel the number of possible cellular states. Many of these changes are associated with altered expression of secreted proteins and other factors involved in cell-matrix and cell-to-cell communication; thus, even presumed cell-autonomous tumor drivers may have non–cell-autonomous effects. Genetically abnormal cancer cells also have a fitness advantage in perturbed microenvironments, such as those created by aging and inflammation, which enables the expansion and further diversification of such cells. Inflammation also promotes metastatic dissemination and outgrowth by promoting angiogenesis and immunosuppression. Thus, tackling metastasis requires a holistic approach that considers the properties of both the host (germline, lifestyle factors and tumor-induced systemic changes) and the tumor for the development of a combination treatment strategy based on this knowledge.

Cynthia L. Sears: cancer and the microbiome

Since rapid and increasingly less expensive technologies for assessing the microbial content of the skin, stool and mucosal microbiota first appeared about 15 years ago, we have witnessed the emergence of a tsunami of data on the composition, structure and function of, in particular, the gut microbiome. In a mouse, the microbiome drives or modifies almost every process or disease state studied so far. In contrast, for humans, while the associated microbial signals can be strong, uncertainty prevails about the contribution of microbes to disease initiation and progression, including, and perhaps particularly, to cancer. We know that an important subset of cancers of global importance have a microbial origin. For example, hepatocellular cancers are caused by the hepatitis viruses B and C; gastric cancer is caused by *Helicobacter pylori* and, in a smaller subset, the Epstein–Barr herpesvirus; Merkel cell carcinoma is caused by the Merkel virus; a subset of cholangiocarcinoma in Southeast Asia is epidemiologically linked to chronic infection with flukes (*Clonorchis sinensis* and *Opisthorchis viverrini*). These, however, are single-microbe-driven tumors and at least do not seem to need microbial communities for disease pathogenesis. In parallel and, thankfully, cure of certain single microbes, such as hepatitis virus C or *H. pylori*, is sufficient to significantly reduce cancer occurrence.

While there is no question that 'on and off' tumor communities differ among most cancers, we lack an understanding of the pro-carcinogenic microbes and communities and the mechanisms by which they may contribute to the TME of specific cancers. Alternatively, microbes could be bystanders, although data from the colorectal cancer (CRC) field challenge this possibility. Microbiome studies, both mouse and human, of CRC indicate that both single pro-carcinogenic bacteria and microbial communities deserve more study. With the rise of CRC globally and the emergence of early-age-onset CRC, much more robust translation of microbiome data to human CRC cohorts (and, by extension, to other cancer cohorts) is needed to understand if certain microbes or communities will provide a path to cancer prevention, either by enhancing early disease detection or by providing a vision for modification

of the pro-carcinogenic microbiome to diminish tumor initiation and progression. So far, sequencing studies alone have not provided sufficiently accurate results for the prevention of CRC, and integrating results from microbial pathogenesis, genomics, metabolomics and other fields is needed to creatively advance the prevention of CRC and other cancers.

Understanding how the microbiome contributes to cancer risk, development, progression, and therapy is a field of opportunity. We could help ourselves move forward by being certain that adequate numbers of patients and controls are presented for publication and by developing standards for evaluating and presenting microbiome studies. So often, differing results obtained with diverse analytical tools from seemingly similar patient groups are presented, although they are frequently assessed with limited clinical metadata. Identifying a way to make microbiome results and conclusions easier to compare across papers would be helpful to the field. We eagerly await the bedside application of microbiome science to advance the prevention of cancer and therapy for people with cancer.

Karen H. Vousden: cancer metabolism

Although genomics has dominated progress in our understanding and treatment of cancer, renewed appreciation of the importance of cancer metabolism in recent years has opened some extremely exciting avenues of exploration. Our progress has been greatly aided by the elegant and detailed delineation of metabolic pathways carried out by biochemists in the last century, allowing us to stand on the shoulders of giants. We now understand that metabolic transformation can contribute to all stages of malignant development, and we have identified oncogenic activity in mutant or overexpressed metabolic enzymes. Systemic metabolic factors can also have a role in promoting the development of cancer. Tantalizingly, the metabolic rearrangements that underpin tumorigenesis may also impose vulnerabilities, such as a limited tumor-cell adaptability or the production of new and possibly toxic metabolites, that could be targeted for therapy. One of the most exciting prospects is the concept that altering systemic metabolism or systemic nutrient levels will drive or enhance therapeutic responses, either by targeting the tumor itself or by eliciting a host response such as immune defense. Particularly appealing is the promise of 'bespoke' dietary modulation: the design of specific diets that are integrated with the genetic alterations and origins of the tumor, along with the mechanisms of action of the treatment. Various approaches are being considered, from broad limitation of certain food groups, such as carbohydrates or proteins, to the removal, or even supplementation, of specific amino acids or sugars. It is still early days, but clinical trials are underway, and rapid progress is being made in delineating the complex tumor–host–therapy interactions. Bespoke dietary control has the potential to augment the response to both conventional therapies and targeted therapies without adding further drug-induced toxicities. Equally important is the notion that prescription of a defined dietary regime will allow patients with cancer to take back control over at least some aspect of their treatment and their lives.

Zemin Zhang: cancer research back at the cellular level

The early years of cancer research were once focused on the cellular level. In the 1850s, Rudolf Virchow first linked the origin of cancer cells to normal cells, which turned into the most well-accepted definition of cancer: a disease of mutant cells that exhibit uncontrolled proliferation and invasiveness. Morphology-based studies of cancer cells dominated the field for more than a century, before the advances in genetics and biochemistry empowered the biological study of cancer. The boom in the understanding of cellular pathways in the 1980s gave cancer research a much needed leap. Over the years, we have accumulated unprecedented knowledge of genes that drive carcinogenesis, cancer progression, metastasis and resistance to therapies, and the paradigm of cancer research gradually shifted from the cellular level to the molecular level. Despite the profound knowledge we have gained from molecular- and pathway-centric studies, a huge gap remains between the molecular-level understanding of cancer pathways and the anticipated intervention solutions.

One possible reason for such disparity between biological knowledge and therapeutic progress may be that we are accustomed to treating clinical tumor samples as a whole, working hard to identify aberrant pathways in tumors and 'silver bullets' that target them. While this idea propelled the development of targeted therapies, it may obscure the fact that different biochemical reactions or signaling pathways occur in different cells. This perception bias has had a deep impact on how targets can be identified. For example, although genes upregulated in tumors may have target implications, we have learned now that many such genes are not expressed by cancer cells at all. Instead, they are expressed by other cellular components in the TME. This intricate tumor ecosystem is so diverse that when we view it as a bulk, we lose not just the knowledge of expression heterogeneity but also vital information about cell types, cell states and intercellular communications. How different cell types work in conjunction with each other to maintain and remodel the microenvironment ultimately shapes therapeutic responses and resistance, as exemplified by the success of immunotherapy. If targeting cancer cells does not cure cancer, the indirect approach of targeting other cells in the TME might improve therapeutic efficacy.

Therefore, more than ever, we need to take up the view of individual cells. If the TME is a battlefield for all anti-cancer therapies, then surveying the field comprehensively is a prerequisite for winning the battle. The recent advances in single-cell sequencing techniques have given us the most powerful approach for this transition of methodology, allowing us to revisit the molecular and genetic processes, back at the cellular level. The ability to study and target any distinct component of the TME will enable us to change the rules of the game fundamentally, for cancer research and, eventually, for the study of all diseases. ❐

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Published online: 13 January 2020
https://doi.org/10.1038/s43018-019-0015-9

Competing interests
The authors declare no competing interests.