Reflections on Advances in Cancer Research in 2024

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Introduction

There have been many impactful advances in basic, translational, and clinical cancer research in 2024. An important mission of *Cancer Discovery* is to ensure the timely dissemination of innovative ways of thinking that will inspire conceptual and technological advances that move the needle forward for the future of cancer prevention, diagnosis, and treatment. Since *Cancer Discovery*'s launch, Research Watch (https://aacrjournals.org/cdnews) – in which the Editors spotlight and summarize recently published articles from other journals each week – has been a popular feature of the Journal and a valuable part of its mission to serve the cancer research community. To further engage with the community in a discussion on recent progress in cancer research, the *Cancer Discovery* Editors asked leading scientists to weigh in on what they thought were the most exciting discoveries of the year. The commentaries below serve to amplify the perspectives of early- and mid-career investigators and showcase the scientific progress that has been made in 2024 and the potential impacts of these advances moving forward in 2025.

REPROGRAMMING THE ANTITUMOR SECRETOME OF SENESCENT CELLS

Katherine M. Aird[1]

Senescence is a metabolically active cell-cycle arrest that plays a pivotal role in various physiologic and pathologic processes. Cancer cells can be induced to senesce through multiple mechanisms, including many chemotherapeutic and targeted therapies currently used in clinical practice. Senescence can be both tumor suppressive and tumor promoting, contingent upon factors such as the magnitude of induction, the timing of the response (acute vs. chronic), and the specific cellular context. This dichotomy poses significant challenges. How can we ascertain whether the induction of senescence within a tumor is beneficial or detrimental? Many protumorigenic effects associated with senescence are attributed to a unique secretory profile known as the senescence-associated secretory phenotype (SASP), which can paradoxically also enhance antitumor immunity. A prominent unresolved issue in cancer senescence research is how to exploit the tumor-suppressive properties of senescence and the SASP while mitigating their tumor-promoting consequences.

A major recent step forward is the discovery of retinoids as senescence-inducing compounds that can rewire the SASP from a protumor to an antitumor program. Retinoids activate retinoic acid receptors, resulting in diverse downstream effects. Research conducted by Colucci and colleagues demonstrated that co-treatment with chemotherapy and retinoids not only augments the proportion of senescent cells but also diminishes the proinvasive and proproliferative paracrine effects associated with the SASP. Notably, this switch of the SASP to an antitumor phenotype enhances intratumoral NK cell infiltration and promotes antitumor immunity. Thus, unlike senomorphics, which suppress the SASP, this approach leverages the antitumorigenic properties of the SASP. Retinoids are currently utilized for the treatment of acne and T-cell lymphoma. In light of the lackluster outcomes from trials of senolytics—therapeutics designed to eliminate senescent cells—this approach represents a significant discovery, offering potential for the rapid implementation of a therapeutic strategy that promotes senescence, reprograms the SASP, and promotes antitumor effects.

Colucci, M, Zumerle S, Bressan S, Gianfanti F, Troiani M, Valdata A, et al. Retinoic acid receptor activation reprograms senescence response and enhances anti-tumor activity of natural killer cells. Cancer Cell 2024;42:646–61.

Cancer Discov 2024;14:2346–51

doi: 10.1158/2159-8290.CD-24-1483

CELL-FREE DNA LIQUID BIOPSY FOR EARLY COLORECTAL CANCER DETECTION

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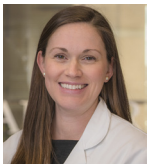
The emergence of liquid biopsy using plasma cell-free DNA (cfDNA) is revolutionizing the early detection of colorectal cancer. This technology allows for the identification of genomic alterations and methylation and fragmentomic patterns from cfDNA in blood plasma, providing a noninvasive method to detect cancer at earlier stages. In 2024, plasma cfDNA-based tests, such as those by Guardant, demonstrated high sensitivity for detecting colorectal cancer, with an accuracy of up to 88%, making them a promising alternative to traditional colonoscopies and making the Guardant Shield assay the first-ever blood test approved by the FDA as a primary screening option for colorectal cancer.

This breakthrough improves accessibility and convenience, offering patients a less invasive option for cancer screening, especially those reluctant or unable to undergo colonoscopies. However, one of the main limitations of plasma cfDNA-based tests is their lower sensitivity for detecting advanced precancerous lesions, such as high-risk adenomas, compared with standard-of-care colonoscopy. For instance, Guardant Health's cfDNA test demonstrated a sensitivity of only 13% for advanced precancerous lesions. Furthermore, although plasma cfDNA tests may provide a more convenient, noninvasive blood-based option, stool-based methods, given their increased proximity to colorectal lesions, may catch these advanced precancerous lesions more sensitively, which is crucial for preventing colorectal cancer development and more closely simulating standard-of-care colonoscopy. As plasma cfDNA tests continue to develop, their sensitivity may be further improved using multiomic technologies that integrate analyses of genomics, epigenomics, fragmentomics, and proteomics. In addition, increasing the sensitivity of plasma cfDNA tests for high-risk adenomas could eventually offer a more holistic screening approach, which could potentially be built into a multicancer early detection assay that includes other cancer types as well.

Chung DC, Gray DM 2nd, Singh H, Issaka RB, Raymond VM, Eagle C, et al. A Cell-free DNA blood-based test for colorectal cancer screening. N Engl J Med 2024;390:973–83.



HARNESSING THE POTENTIAL OF CAR-MONOCYTE CELL THERAPY FOR SOLID TUMORS

Jennifer L. Guerriero[6,7,8]

Monocyte-based cellular therapy is part of a transformative era in cancer immunotherapy. Leveraging the inherent capabilities of monocytes to traffic through circulation, extravasate into tumors, and become mature macrophages that survive and persist in the harsh tumor microenvironment (TME) enables novel therapeutic strategies for solid tumors. The recent development of chimeric antigen receptor (CAR)–expressing monocyte (CAR-mono)–based therapy holds tremendous promise as a weapon against solid tumors. CT-0525 (Carisma Therapeutics), a first-in-class, *ex vivo* gene–modified autologous CAR-mono against HER2, is the first CAR-mono to be evaluated in the solid tumor setting.

Although CAR-T cells have revolutionized the treatment of hematologic malignancies, they have been largely ineffective in solid tumors in part because of poor infiltration and survival in the suppressive TME. Carisma recently demonstrated that CT-0525 efficiently traffics, differentiates into effector proinflammatory CAR-macrophages, and persists with multimodal antitumor mechanisms against $HER2^+$ breast tumor cells in a preclinical model. Clinically, CAR-monos can be manufactured more rapidly with significantly higher cell yield compared with CAR-T cells, enabling higher dosing and repeated administration.

The FDA granted Fast Track designation to CT-0525, which is being investigated in a first-in-human, open-label, multicenter, phase I study in patients with HER2-overexpressing solid tumors (NCT06254807). Safety, tolerability, and manufacturing feasibility will be evaluated as primary outcomes. Secondary outcomes include clinical response, trafficking, TME activation, and T-cell phenotyping and clonality. Initial data are expected to be reported at the end of 2024. Trafficking and antitumor potential of CT-0525 will be of key interest.

Owing to their natural persistence and trafficking patterns, engineered monocytes have the potential to succeed in penetrating and surviving in solid tumors where other cell therapies have failed. In the tumor, the differentiated CAR-macrophages can induce potent phagocytosis and cytotoxicity of cancer cells that can initiate T-cell recruitment, antigen presentation, co-stimulation, and cytokine secretion and ultimately enable epitope spreading to overcome antigen heterogeneity. CAR-monos offer a promising therapeutic opportunity to transform medicine across disease areas.

Abdou Y, Pohlmann PR, Maziarz RT, Murthy HS, Yuan Y, Krishnamurthy A, et al. A phase 1, first-in-human study of autologous monocytes engineered to express an anti-HER2 chimeric antigen receptor (CAR) in participants with HER2-overexpressing solid tumors. J Clin Oncol 2024;42(Suppl 16):TPS2682.

AN EPIGENETIC ECLIPSE UNLEASHES TUMORIGENESIS IN THE ABSENCE OF DRIVER MUTATIONS

Shiri Gur-Cohen[9]

Although cancer has long been considered a genetic disease, early hints surfaced to suggest that tumor progression, metastatic potential, and the ability to evade therapy may extend beyond the genetic code. Epigenetic events are inherently more plastic and dynamic by several orders of magnitude relative to genetic mutations, and it has long been speculated that mutated cells may exploit this epigenetic flexibility to evade selective pressures and grow uncontrollably. This year, a study by Parreno and colleagues challenged the long-standing view that permanent genetic mutations are a requisite for tumorigenesis and instead proposed that transient and reversible disruptions in epigenetic regulation can be sufficient to induce malignant transformation, even in the absence of changes to the DNA sequence. Their work reveals that temporarily depleting the chromatin-remodeling Polycomb complex, a key epigenetic regulator of gene repression, initiates an irreversible neoplastic transformation in *Drosophila* even after Polycomb function is reestablished, suggesting that transient disruptions in gene silencing can permanently ignite a tumorigenic switch.

A short-lived yet impactful "epigenetic eclipse" during which epigenetic changes override normal regulatory mechanisms to trigger tumor initiation might explain cases in which tumors lack definitive genetic drivers. Although it remains to be determined whether transient epigenetic events are sufficient to unleash tumorigenesis in humans, it is tempting to consider how an individual's unique life experiences, such as diet, sleep patterns, and environmental exposures, may render chromatin permissive or restrictive and drive an epigenetic cancer fate. This raises the intriguing possibility that different tissues with distinct chromatin landscapes, such as those with high regenerative demands like the epithelium or more quiescent tissues like muscle, may be primed in their susceptibility to transient epigenetic modifications that drive irreversible oncogenic reprogramming. The possibility that reversible epigenetic disruptions might alone create a critical window of vulnerability in which malignancy can find an opportunity to emerge, leaving a lasting imprint even after the epigenetic shadow has lifted, may profoundly reshape the way we approach cancer prevention.

Parreno V, Loubiere V, Schuettengruber B, Fritsch L, Rawal CC, Erokhin M, et al. Transient loss of Polycomb components induces an epigenetic cancer fate. Nature 2024;629:688–96.

LEVERAGING THE CANCER PLAYBOOK TO IMPROVE T-CELL THERAPIES

Benjamin Izar[10]

T cell–based immunotherapies have revolutionized the treatment of several hematologic cancers and proven efficacious in a subset of patients with treatment-resistant metastatic melanoma. Although some patients experience durable responses to CAR-T cells or autologous tumor-infiltrating lymphocytes, many patients do not, often because of suboptimal activation or poor persistence of T cells. Garcia and colleagues explored an approach akin to a principle of the martial art Aikido: blending with the opponent's energy and, in a circular motion, redirecting it to make the attacker fall from their own force. Specifically, they engineered 71 mutations or gene fusions that drive T-cell malignancies and determined their impact on known hallmarks of T cell–mediated antitumor immunity. This approach led to the identification of *CARD11–PIK3R3*, a gene fusion originally found in a patient with $CD4^+$ cutaneous T-cell lymphoma, which enhanced T-cell therapies via increased signaling of the CARD11–BCL10–MALT1 (CBM) signalosome. The CBM complex is critical for T-cell activation in response to T-cell receptor engagement. Through a series of elegant experiments, they identified the CARD11 domains necessary for this function and demonstrated that the CBM complex enhances activation in an antigen-dependent manner. Expression of *CARD11–PIK3R3* in different generations of CAR-T cells, directed against either CD19 or the tumor-associated antigen MCAM, led to improved T-cell infiltration, persistence, and antitumor activity in both hematologic and solid tumor models. Importantly, *CARD11–PIK3R3* expression did not lead to malignant transformation in long-term *in vivo* studies. Thus, this study represents an important advance and suggests that learning from experiments of nature can be leveraged to potentially develop novel, efficacious, and safe cell therapies.

Garcia J, Daniels J, Lee Y, Zhu I, Cheng K, Liu Q, et al. Naturally occurring T cell mutations enhance engineered T cell therapies. Nature 2024;626:626–34.

BIOMARKERS OF INEQUITY: DISARMING A STRUCTURAL RACISM GIANT

Brittany D. Jenkins[11]

You have heard the statistics. Black women are 41% more likely to die from breast cancer than White women. Black men are two times more likely to die from prostate cancer than their White counterparts. The root cause of these disparities is racism, and it penetrates our Black communities in the United States from every angle. From lack of referrals to and representation in clinical trials, neighborhood disinvestment and environmental injustices, lack of genetic data, and lower receipt of guideline-adherent treatment, Black people in this country have felt the piercing sting of structural and individual-level racism in their everyday lives for centuries. The stress that results from these experiences is not only palpable but measurable. Over the past 5 years, increasing attention has been placed on measuring the impacts of structural racism in the United States. We have now only just begun to develop robust and validated indices that attempt to capture the impact of this multiheaded invisible giant that permeates our health care, education, criminal justice, and economic systems. The development of this measure was highlighted recently in a plenary session at the 2024 AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, in which Lauren Barber described the process of incorporating multiple societal domains (employment, housing, health care, education, etc.) into one index and how effective they were at capturing the intended variable. This complex exposure can now be linked to biological pathways that promote disease—the biomarkers of inequity. Structural racism and biology do not exist in mutual exclusion. We can no longer address these disparities *in silo*; the problem is too complex and too dangerous. We must combine disciplines and expertise from basic science to social epidemiology to medicine, to not only understand but defeat the beast, that is, structural racism.

Barber L. Constructing a multidimensional measure of structural racism [Conference presentation]. In: 17th AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved; 2024 Sept 21–24; Los Angeles, CA. Philadelphia (PA): AACR; 2024.

LEVERAGING GROUNDBREAKING TECHNOLOGIES TO INVESTIGATE METASTATIC SEEDING

Delphine Merino[12,13]

Liver metastases are a common complication of several types of cancers, including colorectal cancer, pancreatic cancer, and melanoma. However, metastasis is considered a highly selective process, and only a small fraction of cancer cells that reach the liver might be able to form macrometastases. The ability of cancer cells to colonize this organ depends on intricate interactions between malignant cells and surrounding nonmalignant cells, such as hepatocytes.

Borrelli and colleagues adopted an innovative cancer-extrinsic approach to reveal the intricacies of this cross-talk. They designed a CRISPR-mediated transcriptional activation screen to perturb hepatocytes *in vivo* and identify the permissive and repressive factors by which these cells control the seeding of metastases. This *tour de force* was accomplished by overexpressing 997 single-guide RNAs in hepatocytes using a transposon-mediated integration. Cancer cells were then introduced into this liver mosaic via intrasplenic injections. The soluble mCherry niche-labeling system was used to identify the perturbed hepatocytes that promote the growth of disseminated cancer cells, as hepatocytes in the neighborhood of growing metastases were labeled by the mCherry secreted by cancer cells.

Several hits were reproducibly identified across independent experiments, revealing the importance of host-derived regulators of colonization, including neurotrophic factors such as plexin B2. Further analysis of patient samples and validation experiments suggested that plexin B2 expressed by metastasis-promoting hepatocytes interacts with class IV semaphorins on cancer cells, activating the transcription factor KLF4 that, in turn, regulates tumor cell epithelialization.

This elegant combination of gene editing and labeling tools not only sheds light on the complex mechanisms involved in the seeding of liver metastases but also holds promise for the future of metastasis research.

Borrelli C, Roberts M, Eletto D, Hussherr MD, Fazilaty H, Valenta T, et al. In vivo interaction screening reveals liver-derived constraints to metastasis. Nature 2024;632:411–8.

CD45-EDITED STEM CELLS UNLOCK UNIVERSAL ANTIBODY-BASED THERAPIES FOR HEMATOLOGIC MALIGNANCIES

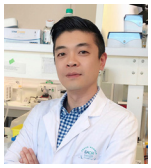
Alejo E. Rodriguez-Fraticelli[14,15,16]

CRISPR-editing of hematopoietic stem and progenitor cells (HSPC) holds tremendous potential for a wide range of therapies. With the FDA approval of gene-edited HSPCs for sickle cell disease last year, the path is clearing for safe CRISPR-edited blood products. One of the most innovative applications is using CRISPR to shield normal HSPCs from leukemia immunotherapy, which targets cancer cells via antibodies or CAR-T cells. Traditional cancer immunotherapies target lineage-specific or stem-cell receptors (e.g., CD33, CD123, and CD19), but these approaches struggle with cancer phenotypic diversity. Broader immune receptor targets, like the universal leukocyte antigen CD45, had been considered too toxic because of its expression in all hematopoietic cells.

This year, Garaudé and colleagues developed a method to efficiently edit CD45, protecting normal HSPCs from anti-CD45 immunotherapy. Critically, CD45 is an essential immune cell receptor, so the edit needed to preserve its normal function while fully evading antibody recognition. To this end, the researchers used adenine base-editing, which increased precision without requiring DNA breaks or homologous recombination. They then developed CIM053, a potent epitope-specific anti-CD45 antibody linked to a selective toxic payload.

In both *ex vivo* and *in vivo* leukemia models, the therapy selectively killed cancer cells without affecting the CRISPR-modified HSPCs, which reconstituted healthy hematopoiesis. Although the study is a strong preclinical success, one leukemia model still relapsed with CD45-low expression, highlighting the need to better understand plasticity and therapy resistance in leukemic cells. Nevertheless, the broad applicability of anti-CD45 approaches, combined with shielded HSPCs, may result in transformative therapies for hematologic patients.

Garaudé S, Marone R, Lepore R, Devaux A, Beerlage A, Seyres D, et al. Selective haematological cancer eradication with preserved haematopoiesis. Nature 2024;630:728–35.



FORESTALLING TUMOR DRUG RESISTANCE: STAYING AHEAD IN CANCER TREATMENT

Shensi Shen[17]

As Charley Lineweaver noted, "Cancer cannot do anything new"; cancer cells are normal cells adapted for survival through genetic or epigenetic changes. Standard treatments are reactive, using cytotoxic drugs that kill most cancer cells but create evolutionary pressure, allowing deadly survivors to evolve and mutate. This leads to therapies being perpetually one step behind cancer. New strategies are thus needed to proactively counter cancer cell evolution and direct it toward suicide. In 2024, Leighow and colleagues explored this idea by creating modular genetic circuits that turn cancer cells into "Trojan horses" that self-destruct. Drawing inspiration from CRISPR-based systems, they developed a dual-switch gene drive. Switch 1 involved a synthetic resistance gene, *EGFR*, with a mutation that confers resistance to osimertinib, fused with a synthetic dimerization domain to enhance oncogenic fitness. This fusion protein is activated by a small-molecule dimerizer, making engineered cells resistant to osimertinib and allowing them to outcompete non-engineered cells. These "Trojan horse" cells then activate switch 2, a suicide switch containing cytosine deaminase, which converts a prodrug into the cytotoxic 5-fluorouracil through gene-directed enzyme prodrug therapy. The researchers also tested various switch variants, showing that a RET kinase mutation as switch 1 and cytosine deaminase as switch 2 effectively eliminated RET^+ thyroid carcinoma cells, whereas CD19 as an alternative switch 2 enhanced antitumor immune activity with blinatumomab and T cells. By preinstalling a synthetic killing switch in tumor cells, this strategy imposes an evolutionary fitness cost on heterogeneous tumor populations, offering a framework to preempt drug resistance. Although further development is needed for clinical application, this research highlights a new therapeutic avenue to influence the evolutionary dynamics of drug resistance in cancer.

Leighow SM, Reynolds JA, Sokirniy I, Yao S, Yang Z, Inam H, et al. Programming tumor evolution with selection gene drives to proactively combat drug resistance. Nat Biotechnol 2024 Jul 4 [Epub ahead of print].

STUDYING TUMOR ARCHITECTURE USING SPATIAL TRANSCRIPTOMICS

Itai Yanai[18]

In glioma, it has been known for many years through histology that structural patterns exist in tumors. The use of novel genomic and spatial tools now holds promise that additional patterns, hitherto hidden to histology, may come to light using an analysis of cellular gene expression states. Greenwald and colleagues examined glioma tumors using both spatial transcriptomics and proteomics and identified three principles of tumor architecture when systematically studying the location of gene programs. First, they describe "state-specific clustering"; that is, that cells in a particular state tend to be proximal to cells also in that state. Second, the authors show that there are pairs of states that tend to be adjacent, which they call "state–state associations." Finally, they define higher-order global organizations, in the form of five layers of associations. Interestingly, when such higher-order organization is present, there is evidence that hypoxia is the driver of this organization; indeed, when hypoxia is not present, for example, as in low-grade isocitrate dehydrogenase–mutant glioma, the authors observed a more disorganized pattern. This work provides exciting evidence that studying spatial organization in tumors using these principles will lead us to identify new aspects of the function and mechanisms underlying the biology of cancer.

Greenwald AC, Darnell NG, Hoefflin R, Simkin D, Mount CW, Gonzalez Castro LN, et al. Integrative spatial analysis reveals a multi-layered organization of glioblastoma. Cell 2024; 187:2485–501.

AUTHORS' DISCLOSURES

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