



Highlights from AACR 2024 annual meeting

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Received: April 20, 2024; Accepted: May 4, 2024; Published Online: May 10, 2024; <https://doi.org/10.59717/j.xinn-med.2024.100072>

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Citation: Wang H. (2024). Highlights from AACR 2024 annual meeting. *The Innovation Medicine* 2(2): 100072.

The 115th annual American Association for Cancer Research (AACR) Meeting, held from April 5-10, 2024, in San Diego, California, attracted over 22,600 attendees. The event featured nearly 7,200 abstracts, 630 speakers and 450 exhibitors, covering diverse areas of cancer research, including population science, cancer biology, translational studies, and survivorship. The theme, "Inspiring Science, Fueling Progress, Revolutionizing Care," set the stage for an event dedicated to catalyzing transformative advancements in cancer research and improving patient outcomes (Figure 1).¹

CHALLENGES

During the conference on basic cancer biology and translational research, discussions prominently featured topics that ranged from the complexity and plasticity of cancer to the detailed characteristics of cancer cells and their interactions within micro- and macro-environmental aspects of tumor ecosystems, this comprehensive exploration shed light on the critical role of understanding tumor mechanisms for identifying potential cure.²

Cancer Complexity

In 2000, Hanahan & Weinberg summarized the 'Hallmarks of Cancer', identifying six physiological changes that drive malignant growth, updated in 2024 by Hanahan et al. to emphasize cancer's systemic nature and interactions with biological and environmental factors.³ From a cellular perspective,¹ Iacobuzio-Donahue explored how subclonal genetic evolution within primary tumors selects for metastatic phenotypes, characterizing the morphological, immunological, and microenvironmental features of pro-metastatic subclones in pancreatic cancer models. Cleveland shared insights into chromothripsis and its role in genome instability, gene amplification and drug resistance. de Lange elucidated how shelterin complex protects telomeres, preventing genomic instability and tumorigenesis, while unveiling the complex relationship between telomere length, cellular immortalization, and cancer risk. Lyden introduced the pivotal role of extracellular vesicles and particles (EVPs) in long-range communication between tumors and distant cells, highlighting their involvement in various systemic effects of cancer. Wang and Burns discussed the epigenetic dysregulation of transposable elements like LINEs and endogenous retroviruses in cancer. Exploring systemic interactions,¹ Goodell shed light on how aging disrupts tissue homeostasis and clonal hematopoiesis, increasing cancer risk. Amit demonstrated how cancer can reprogram and utilize neuronal functions to promote its growth. Schietinger discussed T-cell dysfunction mechanisms in tumor microenvironments. Bullman explored the tumor microbiome's influence on cancer progression and immune system interactions. McAllister unveiled interactions between the microbiome and cancer cells, employing novel methodologies to assess tumor-associated microbes. Lastly, Fendt presented findings on metabolic rewiring, with aspartate driving metastasis via protein translation and extracellular matrix remodeling. These discussions underscored how external and intrinsic factors collectively shape cancer pathology.

Cancer Plasticity

A series talks highlighted the crucial role of cancer cell plasticity, where tumor cells switch between developmental lineages and phenotypic states, conferring therapy resistance and metastatic capabilities.¹ Politi discussed trans-differentiation from adenocarcinoma to squamous or small cell carcinomas post-resistance to tyrosine kinase inhibitors. Graber explored transcription factors ASCL1/2 and "epigenetic loosening" driving de-differentiation following BRAF inhibitors or CAR-T therapy. Gills highlighted lineage switching like pulmonary-to-gastric transitions mediated by pioneer factors FOXA1/2 reprogramming the chromatin landscape. Blanpain presented find-

ings on basal-to-luminal transitions and hybrid states triggered by initiation mutations. Rudin discussed strategies to constrain lineage plasticity in prostate cancer. Klein traced the genomic evolution and phenotypic plasticity of the metastatic seed, revealing disseminated cancer cells with a stem-like, embryonic phenotype that precedes overt metastases and correlates with poor survival. Pe'er elucidated how gene expression and epigenetic plasticity enable metastatic cells to co-opt canonical and non-canonical gene programs to overcome context-dependent challenges, underscoring the need to target this adaptability. These discussions comprehensively explored cancer plasticity's critical role in fostering therapy resistance.

INNOVATIONS

The conference spotlighted cutting-edge technologies set to transform cancer research, with a special focus on spatial biology, organoid models, artificial intelligence, and other innovative tools. as Dr. Mikala Egeblad noted that data-driven tissue profiling in 2D/3D and multi-omics, along with longitudinal "4D" studies, are reshaping our understanding of cancer biology, expanding research possibilities and improving treatment options.²

Spatial biology

Spatial biology emerged as a transformative element reshaping cancer research approaches, emphasizing its potential in elucidating cellular interactions and dynamics within their native tissues.¹ Angelo presented applications in DCIS recurrence prediction, and analyzing nivolumab response in invasive metastatic triple-negative breast cancer. Lundeberg emphasized the use of spatial transcriptomics, combined with sequencing and metabolomics, to meticulously analyze tissue sections, uncovering small, specific cell populations and thus offering a comprehensive view of the cancer ecosystems. Sorger demonstrated the use of advanced 3D profiling techniques in melanoma research, revealing inflammatory signatures in precancerous stages and significant cellular heterogeneity around vasculature in metastatic melanoma. Gottardo discussed the computational hurdles in spatial biology, drawing from his lab's research on immune cell dynamics within tumors and informing tumor immune evasion and potential treatments.

Computational techniques and Artificial intelligence

Computational techniques and AI are revolutionizing cancer research by harnessing large-scale, multi-modal data to integrate pathology, genomics, radiology, and clinical texts into sophisticated models.¹ Presentations spanned topics like Fertig explaining the contrast between data-driven models, which capture cellular states at a specific time, and mechanistic mathematical models, which predict dynamic changes over time. Subbiah chaired a session on AI at the Interface,^{1,4} featuring Giger on AI in medical imaging, data science, and health disparities, Madabhushi on integrating AI in radiology and pathology for affordable and equitable precision medicine, and Clozel on AI in drug development and discovery. In a plenary section, Kather emphasized the rapid advancements in AI's ability to derive prognostic and predictive information from routinely available pathology slides, showcasing the potential of multimodal models, foundation models, and large language models in processing medical data to predict treatment responses and improve patient care. Regev highlighted how breakthroughs in single-cell genomics and spatial transcriptomics are transforming cancer research through precise cellular mapping. She emphasized the "lab in a loop" approach that merges computational work and laboratory research to accelerate drug discovery, this integration of data-driven insights and practical applications is key to advancing cancer treatment.

New models - Organoid

Organoid models showcased their potential to elucidate cancer evolution

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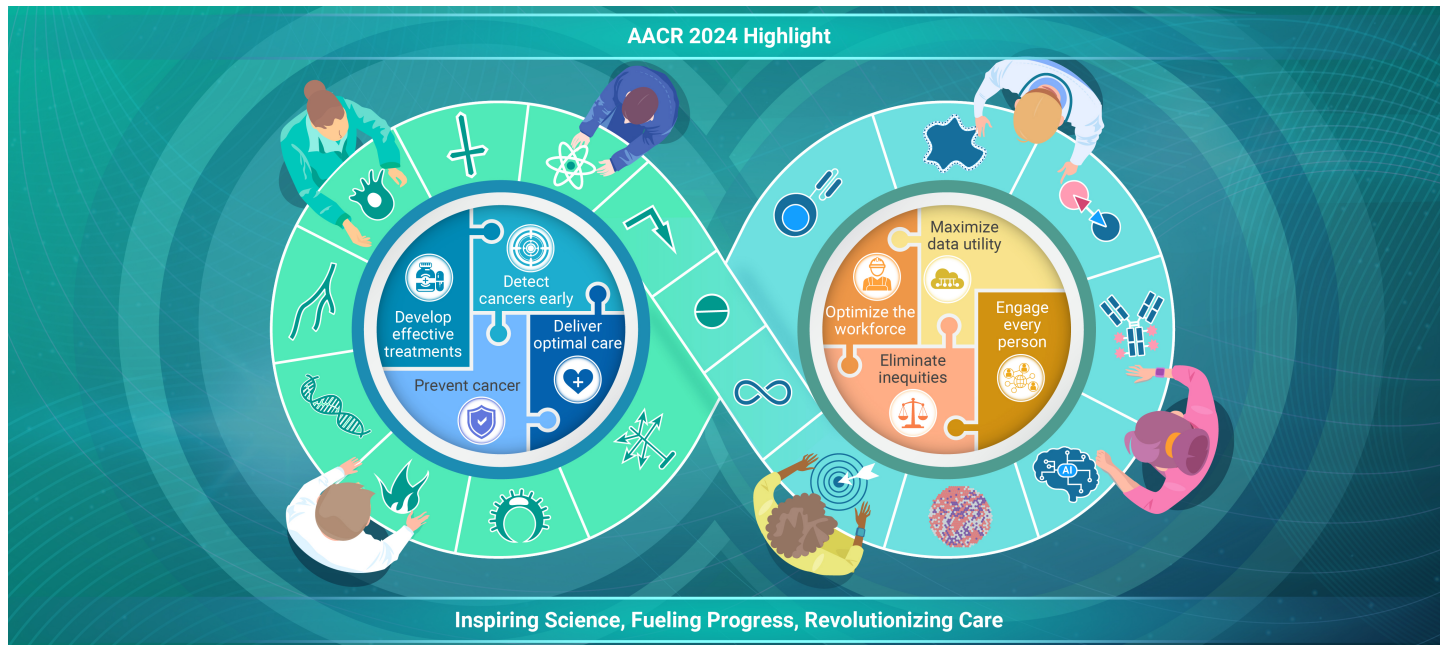


Figure 1. Highlights the key topics and advancements presented at the AACR 2024 Annual Meeting The left concentric circle encompasses the various components of cancer complexity and plasticity, while the right concentric circle showcases the latest innovations in spatial biology, computational techniques, artificial intelligence, organoid models, and groundbreaking therapies such as Ras inhibitors, PROTACs, ADCs, and cancer vaccines. The two central circles represent the essential elements of the National Cancer Plan, with one circle dedicated to health-centric goals and the other focusing on empowering goals.

across various stages. Researchers use niche factors and culture conditions to create organoids from various tumors, enabling detailed studies on tumorigenesis, cell plasticity, therapeutic vulnerabilities, and immune responses, as highlighted by Ganesh using patient-derived organoids. Other researchers apply 3D imaging and transcriptomics in immune-organoid co-cultures to examine T cell-tumor interactions. Rios noted the heterogeneity in rare tumor organoids. Soragni discussed the development of living tumor organoid biobanks for dependency mapping and functional precision medicine, and Garnett introduced the Organoid Cancer DepMap, integrating organoid derivation, genomic analysis, and functional perturbations to map cancer dependencies.

Undruggable targets

This year's conference highlighted the ongoing importance of small molecule drugs in cancer therapy, such as WRN, HPK1, USP1, KIF18A, TEAD, and PARP are receiving significant attention. Special focus was on "undruggable" KRAS, exemplified by the promising anti-cancer effects of RMC-6236 (a RAS(ON) multiRAS inhibitor) and RMC-9805 (targeting the RASG12D mutation) in preclinical and early clinical trials, emphasized the potential of these therapies to revolutionize the treatment of KRAS-driven cancers.¹ In addition, Nobel laureate Carolyn R. Bertozzi also shared advances in using targeted sialidase enzymes to modify tumor glycan structures to boost immune response and inhibit tumor growth, and activate "cold" tumors.¹ Additionally, developments in biologics were presented, including proteolysis-targeting chimeras (PROTACs), antibody-drug conjugates (ADCs), bispecific ADCs, and innovations like glycan-specific ADCs. With several ADCs, including Innovent's IBI343 (anti-Claudin 18.2 monoclonal ADC) and IBI3001 (B7-H3/EGFR bispecific ADC), as well as MacroGenics' glycan-specific ADCs, disclosing promising preclinical data, and IBI343 and Alphamab Oncology's JSKN003 (anti-HER2 bispecific ADC) entering phase III clinical trials. Furthermore, the evolving landscape of cancer vaccines and CAR T-cell therapies was another focal point, signaling their readiness for mainstream application, with presentations covering personalized neoantigen vaccines for pancreatic cancer and HNSCC, shared neoantigen vaccines for various tumor types, and CD70-targeted allogeneic CAR T-cell therapy for advanced clear cell renal cell carcinoma, demonstrating the first complete response in solid tumors.¹ These innovative approaches in small molecule inhibitors, biologics, and cell-

based therapies, capturing their potential to revolutionize cancer treatment and transform the standard of care.

GOALS

The AACR meeting highlighted the National Cancer Plan's goals, aligned with the Cancer Moonshot, to reduce cancer mortality by 50% within 25 years. The plan outlines health-centric goals like prevention, early detection, effective treatments, and optimal care, as well as empowering goals such as maximizing data utility, eliminating inequities, optimizing the workforce, and engaging society.⁵ However, robust funding and innovative collaborations among diverse stakeholders are crucial for driving progress.

The AACR advocates for improved training to help researchers communicate better within the scientific community and with the public. This includes promoting interdisciplinary collaboration and overcoming technology-related communication barriers. Additionally, the priority is effective communication with the public, focusing on addressing misinformation and educating various groups through clear language, engaging storytelling, and effective use of social media.

These plans and advocacy efforts are designed to benefit not just a single nation, but researchers and patients across global communities. An open, innovative collaborative approach that engages nations worldwide will be key to advancing cancer treatment and patient care universally, enhancing well-being of people around the world.

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DECLARATION OF INTERESTS

The author declares no competing interests.