Cracking Cancer's Drug Resistance Code: How Omics is Shaping the Future of Precision Medicine

By Shannen Arviola

Cancer is one of the leading causes of death worldwide, responsible for nearly 10 million fatalities in 2020 – about one in six deaths, according to the WHO.[1] Cancer is a disease in which abnormal cells grow uncontrollably, usually spreading beyond their normal boundaries to invade other areas, even moving to other organs. It can originate in any organ or tissue of the body.[2] Despite billions of dollars invested in cancer research, the disease remains a profound mystery to the scientific community, with many aspects still not fully understood.[3]

In spite of the continuous development of cutting-edge cancer therapies, imagine a scenario where cancer cells become resistant to treatment–they simply do not respond to therapy, no matter how effective it is. In this battle against cancer, drug resistance is the silent enemy that undermines even our most potent therapeutics.[4] When cancer cells become less responsive or completely resistant to the effects of treatments, major challenges in cancer therapy arise, which often lead to treatment failure, disease progression, and ultimately poorer outcomes for patients.[2,3] Drug resistance, which can either exist before treatment or can occur after therapy, accounts for most relapses of cancer and is also responsible for 80-90% of cancer-related deaths.[5,6,7]

What if the key to understanding drug resistance in cancer lies in a much deeper understanding of cancer at a molecular level? Multi-omics is a holistic approach that combines data from multiple levels of biology, such as genomics (genome), metabolomics (metabolites), transcriptomics (RNA transcripts produced by the genome), epigenomics (heritable changes in gene expression that are not caused by DNA changes), proteomics (proteins), and other omics disciplines.[8,9] It is an integration of various omics fields, which presents enormous potential in advancing our understanding of drug resistance in cancer. Multi-omics offers a more comprehensive understanding of molecular changes that affect normal development, cellular responses, and diseases – including cancer.[8]

Challenge of Drug Resistance in Cancer

For many patients, a major challenge arises when a treatment that was once effective suddenly stops working. How is this possible? Some cancer cells are inherently resistant to treatment from the onset; others can adapt through various mechanisms, utilizing the body's own defenses to develop resistance.[10]

A notable barrier in understanding cancer is its complexity and heterogeneity. Cancer can originate in any organ, with the cell type involved varying according to the tissue of origin. Further complicating this is the fact that significant cellular heterogeneity is often exhibited within a single tumor, regardless of its origin. Aggravating the problem, patients with the same cancer diagnosis may have tumors with distinct molecular profiles. This heterogeneity complicates diagnosis, prognosis, and treatment, making the tumor more adaptable, aggressive, and resistant to therapy.[5,10]

Intrinsic resistance refers to the natural resistance cancer cells have to treatment before therapy even begins. This can arise from pre-existing genetic mutations that reduce responsiveness to therapy.[5,6] For instance, mutations like overexpression of cell growth proteins (e.g., *HER2*) in gastric cancer can make cells resistant to cisplatin therapy by promoting epithelial-mesenchymal transition.[6] That process increases cancer cell survival and drug resistance. Additionally, tumors are often heterogeneous with resistant subpopulations such as cancer stem cells that survive treatment and lead to relapse.[6] Intrinsic resistance can also be driven by activation of defense mechanisms like ATP-binding cassette (ABC) transporters or the glutathione system, which help cancer cells expel or detoxify drugs, further reducing the treatment's efficacy.[6]

Meanwhile, ***acquired resistance*** develops over time when cancer cells initially respond to treatment but gradually become resistant.[5,6] This can occur through mutations or changes in the expression of drug target genes, which reduce drug efficacy. For example, in

https://doi.org/10.29173/hsi491
Received 28 March 2025
Accepted 1 July 2025

chronic myelogenous leukemia, an alteration mutation in the *BCR-ABL* gene changes the drug-binding site, making imatinib less effective.[6] Another factor in acquired resistance is changes in the tumor microenvironment (TME), where interactions between cancer cells and stromal cells, through exosomes, can lead to resistance.[6] Importantly, acquired resistance can develop as cancer cells accumulate new mutations during therapy, allowing them to evade the effects of initially effective treatments.[5,6]

Cancer resistance to chemotherapy is commonly observed among nearly all medications used to treat the deadliest cancers.[7] Some of these include doxorubicin, paclitaxel, 5-fluorouracil, and carboplatin, wherein resistance is linked to cancer recurrence, poorer prognosis, and shorter survival in breast cancer patients.[7] Resistance to drugs such as cisplatin and oxaliplatin leads to similar outcomes in gastric cancer.[7]

While acquired resistance to therapy has long been recognized as a challenge to achieving fully effective cancer treatments, it is becoming an increasingly critical issue even for new molecular-targeted drugs.[11] With the rise of target chemotherapy, drugs are designed to block specific molecules and target metabolic pathways involved in cancer cell growth, such as imatinib (Gleevec) that targets *BCR-ABL* gene in chronic myeloid leukemia.[11] Targeted therapies aim to provide maximum efficacy with minimal toxicity compared to traditional cancer therapies. In theory, the more precise a drug is, the lower the likelihood of resistance. Since molecularly-targeted drugs focus specifically on particular cancer targets, they allow for effective treatment at much lower doses.[11] Despite their potential, both targeted and traditional therapies face challenges with intrinsic and acquired drug resistance.[5,6,7,11]

What if the key to overcoming cancer lies in leveraging existing technologies and combining their collective power to provide us with data, analyses, and insights that can help us unravel the code of resistance? In this fight against cancer, multi-omics approaches are emerging as a crucial tool in tackling this complex challenge.

Multi-Omics – A New Approach to Cancer

The Canadian Institutes for Health Research (CIHR) has been actively supporting multi-omics research through its various funding initiatives. Under its newly launched "Team Grants: Embracing Diversity to Achieve Precision and Increase Health Equity" program in 2024, the general omics pool is expected to take up to three grants, amounting to up to $2,000,000 per grant.[12] Additionally, in a collaboration with Genome Canada, CIHR co-funds projects under Genome Canada's "Canadian Precision Health Initiative," which aims to sequence genomes of at least 100,000 Canadians.[13] This funding supports cancer research by generating population-level genomic and multi-omics data.[13]

Why are we heavily investing in multi-omics, and what potential does it hold for cancer research? Using multiple biological data types from a single individual allows for a more complete picture of the molecular factors and cellular processes influencing their health and disease state. This approach uncovers both genetic and non-genetic contributions to overall health and disease.[15] For example, examining the genome, RNA transcripts, proteins, and metabolites involved in cellular functions, as well as changes in gene expression, gives us a holistic view of complex diseases like cancer – far beyond what a single data type could reveal.[14,15]

Significant advancements in high-throughput technologies allow detailed analyses at molecular, cellular, and tissue levels. Whole exome sequencing (WES) and whole genome sequencing (WGS) provide us with data on gene expression. Single-cell technologies provide us with insights into gene activity and cellular characteristics. Moreover, mass spectrometry enables accurate detection of proteins and metabolites.[15]

Cancer, being a complex disease, often involves the interaction of multiple molecular pathways. This includes not only genetic mutations but also changes in gene expression, DNA alterations, metabolic abnormalities, disrupted signaling pathways, and environmental factors – all of which require insights from various fields of omics.[15] Multi-omics helps us identify the key players involved in cancer development, progression, and treatment.[15,16] In summary, multi-omics provides a wealth of valuable information that offers new knowledge about cancer that we've never had before.

The Role of Multi-Omics in Overcoming Cancer Drug Resistance

Researchers from Peking University Cancer Hospital in Beijing used multi-omics to characterize the molecular

features of gastric cancer and its correlation with responses to neoadjuvant chemotherapy (chemotherapy before primary surgery).[16] They identified a critical research gap: neoadjuvant chemotherapy is often underutilized due to a limited understanding of the drug resistance mechanisms involved.[16] To address this, the team applied a multi-omics approach, combining WES, WGS, and RNA sequencing to identify various molecular aberrations. This integrated analysis of diverse biological data sets provided high-confidence results.[17] Their findings revealed that mutations in the *C10orf71* gene were linked to treatment resistance, with drug response data suggesting potential inhibition of the cell cycle.[16] Additionally, their research demonstrated that neoadjuvant chemotherapy alters tumor-immune signaling and reshapes the TME. This work offers valuable insights for developing precision neoadjuvant treatment regimens.[16]

Researchers from Samsung Medical Centre and Sungkyunkwan University School of Medicine in Korea used a multi-omics approach to investigate drug resistance in breast cancer, focusing on resistance to CDK4/6 inhibitor therapy combined with endocrine therapy.[17] Palbociclib, a CDK4/6 inhibitor, blocks cell cycle progression and reduces cell proliferation when combined with anti-estrogen agents.18 However, about 25% of patients show no response, and others eventually experience cancer progression.[19] The researchers aimed to identify patients most likely to benefit from treatment and uncover therapeutic targets to overcome resistance. By integrating genomics and transcriptomics, they identified molecular features linked to acquired resistance, including mutations in *TP53*, *BRCA1/2*, and other genes associated with homologous recombination deficiency (HRD).[17] Their study suggested that a combined TP53/HRD-high mutant cluster could serve as a new biomarker for identifying patients with poor responses to CDK4/6 inhibitors, who may benefit from PARP inhibitors or other DNA-targeting therapies. Additionally, tumors analyzed after progression were found to have mutations in ***ESR1***, *RB1*, and *KMT2C*, which contributed to resistance.[17] This multi-omics approach helps identify patients who would benefit most from treatment and uncovers potential targets to overcome resistance; ultimately it aims to improve breast cancer treatment and outcomes.[17]

Due to the complex nature of cancer, high-throughput analyses like multi-omics function as a powerful tool in combating the disease. By understanding drug resistance, we could identify new drug targets that could lead to the development of more effective treatments.[17,19]

The Future of Cancer Treatment with Multi-Omics

The full potential of multi-omics remains largely untapped. With the rapid evolution of emerging technologies and the integration of artificial intelligence (AI), we expect to make significant strides in cancer research. AI can accelerate data analysis, allowing for vast datasets to be processed in a fraction of the time, offering more generalizable results.[20] This faster analysis will hopefully enable the medical community to improve patient outcomes more quickly, which is a critical factor in cancer treatment.[20] By harnessing the power of multi-omics, we are unlocking new doors for precision medicine – a world where cancer treatments are tailored to the individual patient.

Multi-omics data can reveal how mutations and gene expression influence treatment responses, particularly in immunotherapy.[9,21] Current researchers are applying single-cell multi-omics to study patient responses to therapies like checkpoint inhibitors. This allows the identification of biomarkers that predict treatment efficacy and uncover mechanisms of resistance.[21] Machine learning also plays a crucial role in analyzing the vast multi-omic datasets, enabling the identification of relevant gene sets and pathways that can lead the way to personalized treatment strategies.[21] Despite these advances, the integration of diverse multi-omic data remains a challenge, where more sophisticated bioinformatics tools are needed to make sense of the data.[8,9,21]

This is an exciting time to leverage the power of multi-omics to crack the code of drug resistance and revolutionize the future of cancer care. Looking ahead, multi-omics could become a routine tool for cancer diagnosis, prognosis, and personalized treatment.[21] It would allow deeper understanding of tumor dynamics and could help align therapies with the optimal patient population.[21] As the cost of sequencing decreases and data integration improves, multi-omics will likely become integral to clinical cancer care, offering a holistic view of cancer and moving personalized treatment closer to reality.[8,9,21]

Shannen Arviola is an incoming third-year Doctor of Pharmacy student at The University of British Columbia. She has always been involved in research, across various fields like oncology, pharmacogenomics, and epidemiology.

References

1. World Health Organization. Cancer. World Health Organization; 2025. https://www.who.int/news-room/fact-sheets/detail/cancer
2. World Health Organization. Cancer. World Health Organization; 2019. https://www.who.int/health-topics/cancer#tab=tab_1
3. Sullivan R. The Gross Imbalances of Cancer Research Must Be Addressed. Nature. 2023 Sep 6;621(7977):S15–5. https://www.nature.com/articles/d41586-023-02609-2
4. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The Different Mechanisms of Cancer Drug Resistance: a Brief Review. Advanced Pharmaceutical Bulletin. 2017 Sep 25;7(3):339–48. doi: 10.15171/apb.2017.041
5. National Cancer Institute. Why Do Cancer Treatments Stop Working? - National Cancer Institute. www.cancer.gov. 2016. https://www.cancer.gov/about-cancer/treatment/research/drug-combo-resistance
6. Wang X, Zhang H, Chen X. Drug Resistance and Combating Drug Resistance in Cancer. Cancer Drug Resistance. 2019 Jun 19;2(2):141-160. doi: 10.20517/cdr.2019.10
7. Ramos A, Sadeghi S, Tabatabaeian H. Battling Chemoresistance in Cancer: Root Causes and Strategies to Uproot Them. International Journal of Molecular Sciences. 2021 Aug 31;22(17):9451. doi: 10.3390/ijms22179451
8. Ford, T. What Is Multiomics? Nautilus Biotechnology. 2023 May 23. https://www.nautilus.bio/blog/what-is-multiomics/
9. Illumina. Multiomics offers a holistic view of biology. illumina. 2025. https://www.illumina.com/techniques/multiomics.html
10. Levantini E. Novel Therapeutic Targets in Cancers. International journal of molecular sciences. 2023 Sep 28;24(19):14660–0. doi: 10.3390/ijms241914660
11. Nikolaou M, Pavlopoulou A, Georgakilas AG, Kyrodimos E. The Challenge of Drug resistance in Cancer treatment: a Current Overview. Clinical & Experimental Metastasis. 2018;35:309–18. 10.1007/s10585-018-9903-0
12. Canadian Institutes of Health Research. Notice of Upcoming Funding Opportunity - Team Grants: Embracing Diversity to Achieve Precision and Increase Health Equity. CIHR. 2024 [cited 2025 Mar 5]. https://cihr-irsc.gc.ca/e/53589.html?utm_source
13. Chibambo, R . Canada launches $200M genomics data initiative to drive precision health and economic growth.. GenomeCanada. 2025 [cited 2025 Mar 5]. https://genomecanada.ca/canada-launches-200m-genomics-data-initiative-to-drive-precision-health-and-economic-growth/
14. Heo YJ, Hwa C, Lee GH, Park JM, An JY. Integrative Multi-Omics Approaches in Cancer Research: from Biological Networks to Clinical Subtypes. Molecules and Cells. 2021 Jul 9;44(7):433–43. doi: 10.14348/molcells.2021.0042
15. Chakraborty S, Sharma G, Sricheta Karmakar, Banerjee S. Multi-OMICS Approaches in Cancer biology: New Era in Cancer Therapy. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2024 June;1870(5):167120–0. doi: 10.1016/j.bbadis.2024.167120
16. Li Z, Gao X, Peng X, May Chen MJ, Li Z, Wei B, et al. Multi-omics Characterization of Molecular Features of Gastric Cancer Correlated with Response to Neoadjuvant Chemotherapy. Science Advances. 2020 Feb 26;6(9)eaay4211. doi: 10.1126/sciadv.aay4211
17. Yeon Hee Park, Im S, Park K, Wen J, Lee KH, Choi Y, et al. Longitudinal multi-omics Study of Palbociclib Resistance in HR-positive/HER2-negative Metastatic Breast Cancer. Genome Medicine. 2023 Jul 20;15(55). doi: 10.1186/s13073-023-01201-7
18. Cancer Care Ontario. Drug Formulary - Palbociclib. 2025. https://www.cancercareontario.ca/en/drugformulary/drugs/monograph/44456
19. Migliaccio I, Bonechi M, McCartney A, Guarducci C, Benelli M, Biganzoli L, et al. CDK4/6 inhibitors: a Focus on Biomarkers of Response and post-treatment Therapeutic Strategies in Hormone receptor-positive HER2-negative Breast Cancer. Cancer Treatment Reviews. 2021 Feb 1;93:102136. doi: 10.1016/j.ctrv.2020.102136
20. He X, Liu X, Zuo F, Shi H, Jing J. Artificial intelligence-based multi-omics Analysis Fuels Cancer Precision Medicine. Seminars in Cancer Biology. 2023 Jan;88:187–200. doi: 10.1016/j.semcancer.2022.12.009
21. Illumina. Big Picture Oncology through Multi-omics. Nature Research Custom Media. [cited 2025 Mar 5]; https://www.nature.com/articles/d42473-020-00119-7