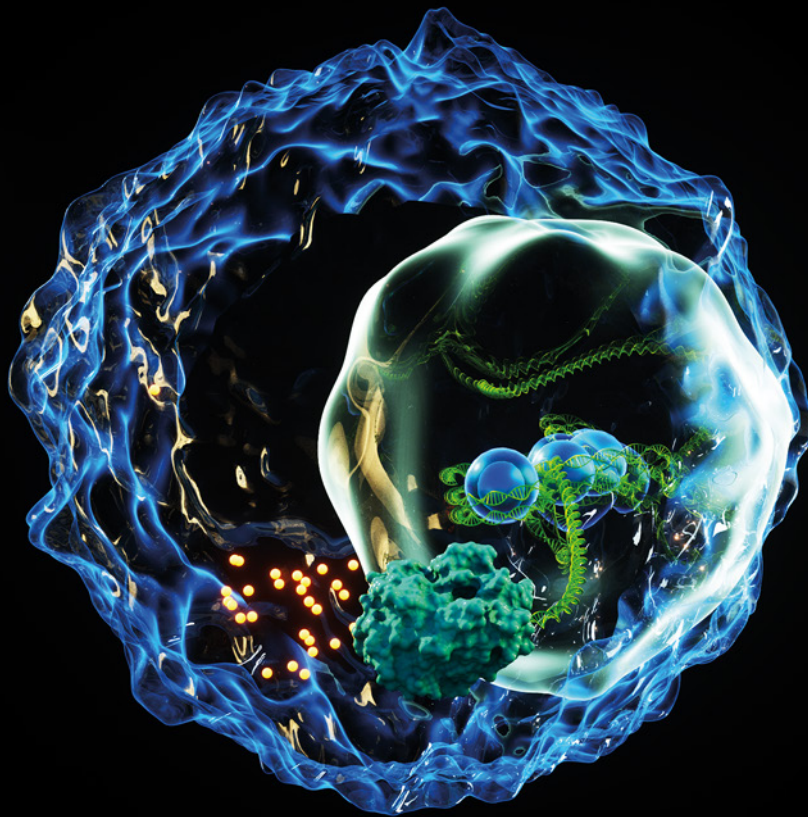


BIGGER PICTURE ONCOLOGY THROUGH MULTI-OMICS

Researchers are using every piece of molecular data available to characterize tumours, identify therapeutic targets, and make precision medicine more precise.



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Researchers are using every piece of molecular data available to characterize tumours, identify therapeutic targets, and **MAKE PRECISION MEDICINE MORE PRECISE.**

DNA mutations are the hallmarks of cancer. Some mutations, termed drivers, give tumours a selective growth advantage and promote cancer development. Mutations in the *BRCA* gene are one example; knowledge of these drivers can guide treatment decisions.

Then there are passenger mutations, which seem to be important but do not directly drive cancerous growth, as well as other molecular changes at the RNA and protein levels. These mutations all play a role in deregulating cell metabolism, stimulating cell growth and promoting metastasis, but their exact contributions are largely unclear.

In recent years, next-generation sequencing has become better at identifying both the mutations in DNA and the changes in gene expression and post-translational modifications. Detecting all these cancer hallmarks — in the epigenome, transcriptome, proteome and metabolome — is giving researchers more data

to understand the disease.

“Multi-omics data are offering the opportunity to redefine the precision oncology paradigm,” says Francesca Finotello, a bioinformatician at the Biocenter, Innsbruck Medical University of Innsbruck, Austria. “We are moving from a simplistic, genomic-focused implementation towards one based on a more holistic and comprehensive vision of the tumour microenvironment.”

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Each type of omic data adds to the list of molecular differences associated with cancer, revealing useful markers of disease process and providing insights into biological pathways.

But individual strands of omics data are not sufficient to reveal the causal relationship between molecular signatures and the manifestation of cancer.

Approaches that integrate different omics data types have the potential to uncover those causative changes and to improve understanding of the variability in treatment response, two major challenges in oncology.

“The long-term vision is to link the extremely detailed molecular phenotypes to outcome information, and use that to stratify patients and improve treatments,” explains William Greenleaf, a geneticist and biophysicist at Stanford University in California.

Thanks to multi-omics, researchers can get a bigger picture of all the different ways in which cellular dysfunction can cause cancer. And, as Greenleaf reasons, “hopefully there is a finite number of these ways and it will be pretty reasonable to classify people with respect to best treatment practices”.

Finding cancer's molecular fingerprint

Cancer researchers can now combine DNA sequencing data with data from other sequencing modalities measuring gene expression, gene activation and protein levels. This can be done in a population of cells (bulk) or, as is increasingly popular, in single cells (sc).

A recent study¹ by Greenleaf and colleagues combined scRNA-seq, scATAC-seq (assay for transposase-accessible chromatin using sequencing), and scCITE-

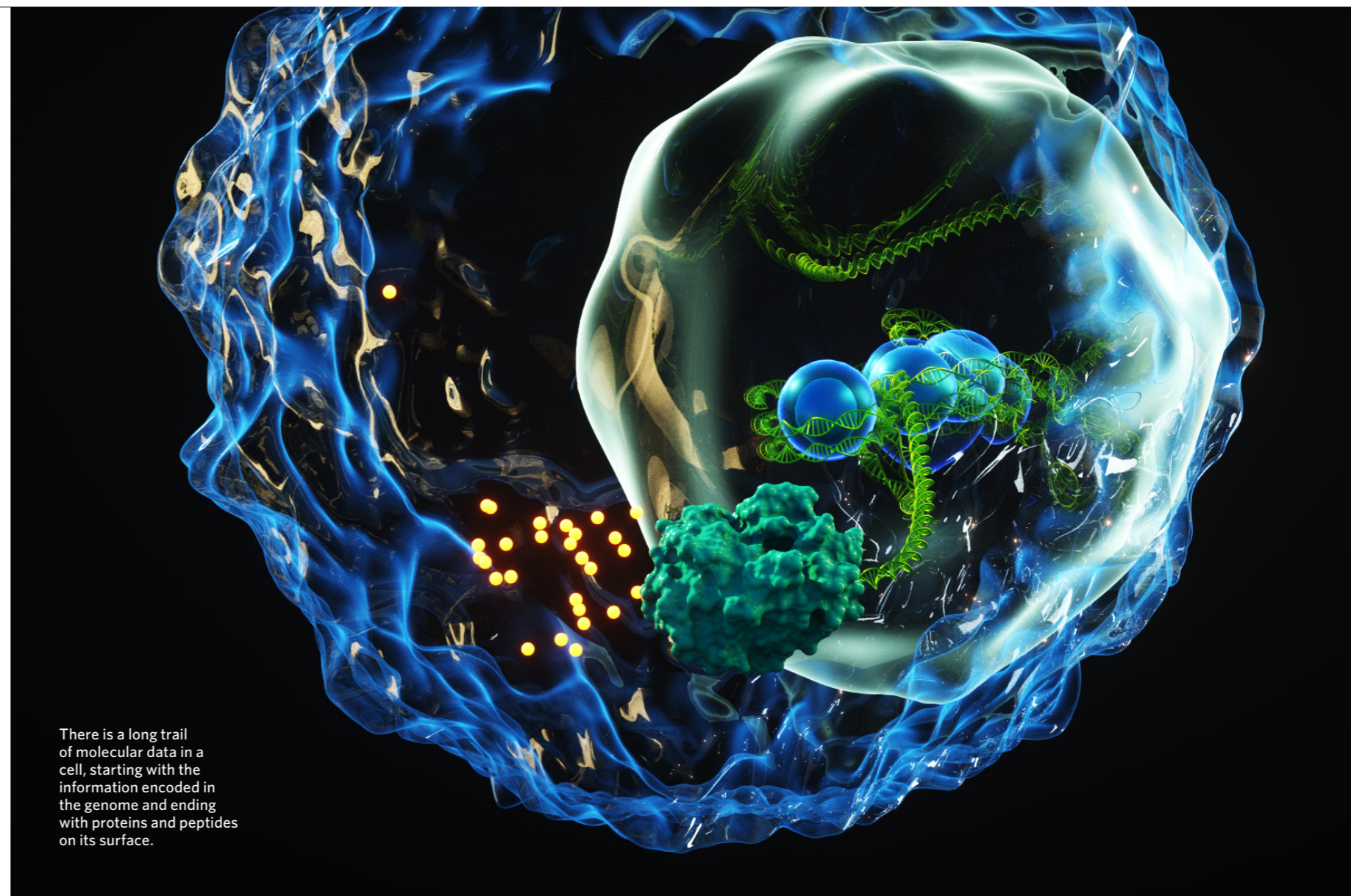
seq (cellular indexing of transcriptomes and epitopes by sequencing) to read the transcriptome, epigenome and surface protein markers (respectively) of single blood cells. By comparing these omics data across healthy and leukaemic cells, the team could identify cancer-specific regulatory processes. “Having a picture at the single-cell level of all of these components gives you a powerful window into the regulation of blood differentiation in normal cells and in disease,” Greenleaf explains.

Despite significant differences in transcription and epigenetic regulation across patients, Greenleaf's team found some relatively conserved signatures within patient subpopulations. They identified *RUNX1* as a key regulator of leukaemia-specific genes, suggesting that this approach could identify new candidates for therapeutic intervention. Working with The Cancer Genome Atlas Analysis Network, Greenleaf is starting to apply multi-omic technologies to characterize other types of cancer cells.

This is the approach being used to refine the data in the Cancer Cell Line Encyclopedia (CCLE). CCLE is a collaborative project between the Broad Institute, the Novartis Institutes for Biomedical Research and the Genomics Institute of the Novartis Research Foundation. CCLE recently expanded the genetic and pharmacological characterization of more than 1,000 human cancer cells to include transcriptomic, epigenomic, proteomic and metabolomic data². This updated resource, which is freely available, will enable

more comprehensive analyses of the links between cancer cells' molecular profile and drug sensitivity, improving drug discovery efforts in industry and academia.

Multi-omics can also be used to compare preclinical models with patient samples. In order to translate drug candidates into clinical compounds, these preclinical models should resemble the relevant patient population as closely as possible. Bin Chen, a data scientist at Michigan State University, explains that by comparing the molecular features of these models with

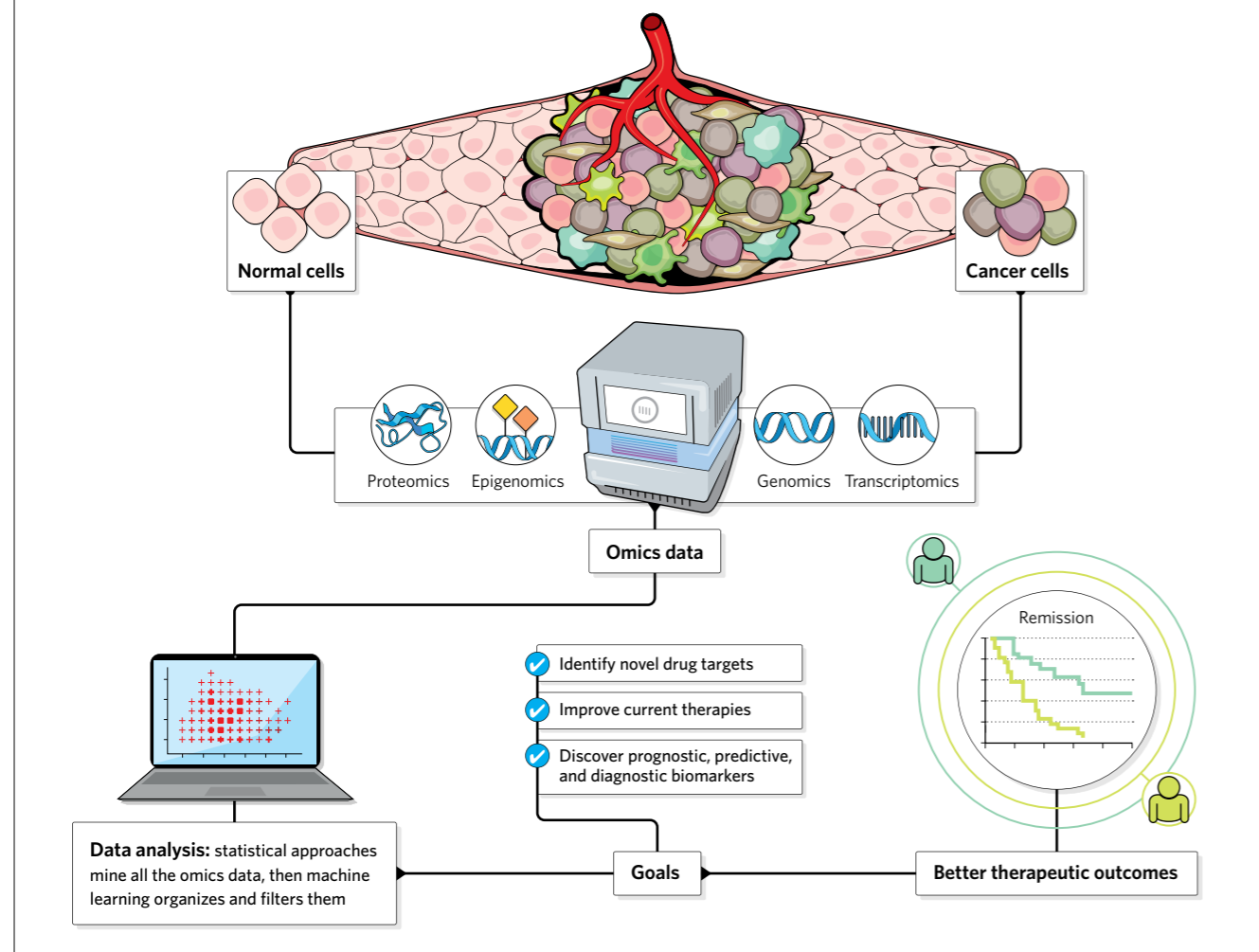


There is a long trail of molecular data in a cell, starting with the information encoded in the genome and ending with proteins and peptides on its surface.

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From the genome onwards, gathering all molecular data from cancerous cells and comparing it with those from healthy cells can provide researchers and clinicians with valuable insights.



patient samples, researchers can choose the model with the most similarities. His team recently showed that the MDA-MB-231 cell line, the most commonly used human cancer cell line for metastatic breast cancer research, bears few genomic similarities to basal-like metastatic breast cancer patient samples³. This study highlights the need for alternative models for studying this type of breast cancer.

Chen's team is also using these techniques for drug discovery. "We are using analyses of multi-omic data to identify drug-like compounds that can reverse a disease expression signature," Chen says. His team compares multi-omics data from patient samples and from preclinical models treated with small molecules. This approach allows them to examine the

effect of drug candidates on multiple molecular markers of disease simultaneously. In a bioinformatics search of existing drug candidates that might be effective in liver cancer, they identified three anthelmintics that reversed the altered expression of several genes in liver cancer cells. These agents could have more potential than ones that target a single molecular alteration⁴.

Improving cancer treatments

Multi-omics data from cancer cells can also help explain their response to treatment and guide the development of therapies that will be more effective for them. Mutation-associated cancer antigens (neoantigens) are informing the development of personalized anticancer vaccines and cellular immunotherapies, but their efficacy may not just depend

on tumour-associated mutations. Differences in the expression of a particular gene or in protein levels could also affect treatment response.

"The mechanisms explaining why some patients respond to immunotherapy and others don't remain elusive," says Diether Lambrechts, cancer geneticist and Director of the VIB-KU Leuven Center for Cancer Biology in Belgium. He is applying single-cell multi-omics in clinical trials of checkpoint inhibitors, drugs that interfere with the mechanism cancer cells use to evade the immune response, to understand why some patients respond and some don't.

Lambrechts' team profiles the transcriptome, epigenome and cell-surface markers of immune cells in tumour samples before and during treatment, and after relapse (if any). In this way, they can see whether the treatment is activating the cells and how it affects their interactions in the tumour microenvironment. "Single cell analysis is key to identifying biomarkers that will help to predict patient response," he says.

Multi-omic biomarkers that tally with treatment response are potential regulatory switches that mediate

"Our ultimate goal is to make tumours more responsive to treatment," he explains. In the first year of this four-year project, his team collected samples from 100 patients and is in the process of applying machine learning to analyse the huge datasets they are generating. Machine learning methods can be used to organize and filter multi-omic data from a patient in ways that make them useful to physicians, without the assumptions attached to traditional statistical methodologies. This approach can quickly identify the gene sets or pathways most relevant to a particular type of cancer, and validate multi-omic biomarker panels to navigate patients to their best treatment options.

Innsbruck bioinformatician Finotello and colleagues are also using machine learning. They analysed multi-omic data from The Cancer Genome Atlas, representing more than 8,000 samples across 20 types of solid cancer. Their goal was to identify which molecular signals are most likely to trigger an immune response. Their findings, available in The Cancer Immunome Atlas could be used to predict the susceptibility of a particular tumour to immunotherapy⁵.

"Multi-omics is providing new insights into the mechanisms of resistance," says Finotello. "Single-cell multi-omics technologies are allowing us to characterize the molecular features that are driving the fate, and regulating the function of, cells in the tumour microenvironment." This knowledge will help design more effective personalized treatments and combination therapies.

What's next for multi-omics
Multi-omics methods are generating vast amounts of data of many different kinds. Integrating them to obtain biologically meaningful insights is one of the biggest challenges, says Finotello. Researchers need sophisticated and robust computational strategies that

from single cells, or from smaller amounts of sample, in less time, and integrate the data in a standardized way. This requires further technological improvements (to decrease sample processing and measurement time, for example) and sharing of integration strategies.

"WE ARE ONLY A FEW YEARS OFF TRANSLATING GENOME-SCALE DATA SETS INTO CLINICALLY APPLICABLE KNOWLEDGE."

consider the particular features of each of the different data modalities.

"We are still in the process of data gathering and developing bioinformatic tools to understand the molecular dysfunctions that are brought about by cancer-associated mutations," Greenleaf says. He and other researchers in this field, are excited about the possibility of combining single-cell multi-omics with spatial information, using multiplexed imaging, to reconstruct the tumour architecture and investigate intercellular communication.

Thanks to the decreasing cost of sequencing technologies and the speed at which they generate data, a growing number of researchers are starting to combine multi-omics with genetic or drug perturbations. "This will uncover the dynamic properties of different cells in the tumour microenvironment, which cannot be extracted from 'static' omics data," says Finotello.

Ultimately, multi-omics could be used in the clinic as a reliable tool to diagnose cancer or determine a patient's prognosis. For this to happen, researchers will need to be able to gather more information

As the cost of omics technologies continues to decrease, more labs will be able to perform multi-omic sequencing in samples under various conditions. "In the coming years, I expect longitudinal multi-omics profiling of patients, along with their imaging and clinical data, to be commonly employed to understand disease," Chen predicts.

The once distant vision of personalized cancer care is moving closer, and it no longer relies on one type of data. "By integrating multi-omic data, we can get a full picture of a cancer cell's molecular profile," says Lambrechts. "We are only a few years off translating genome-scale data sets into clinically applicable knowledge."

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