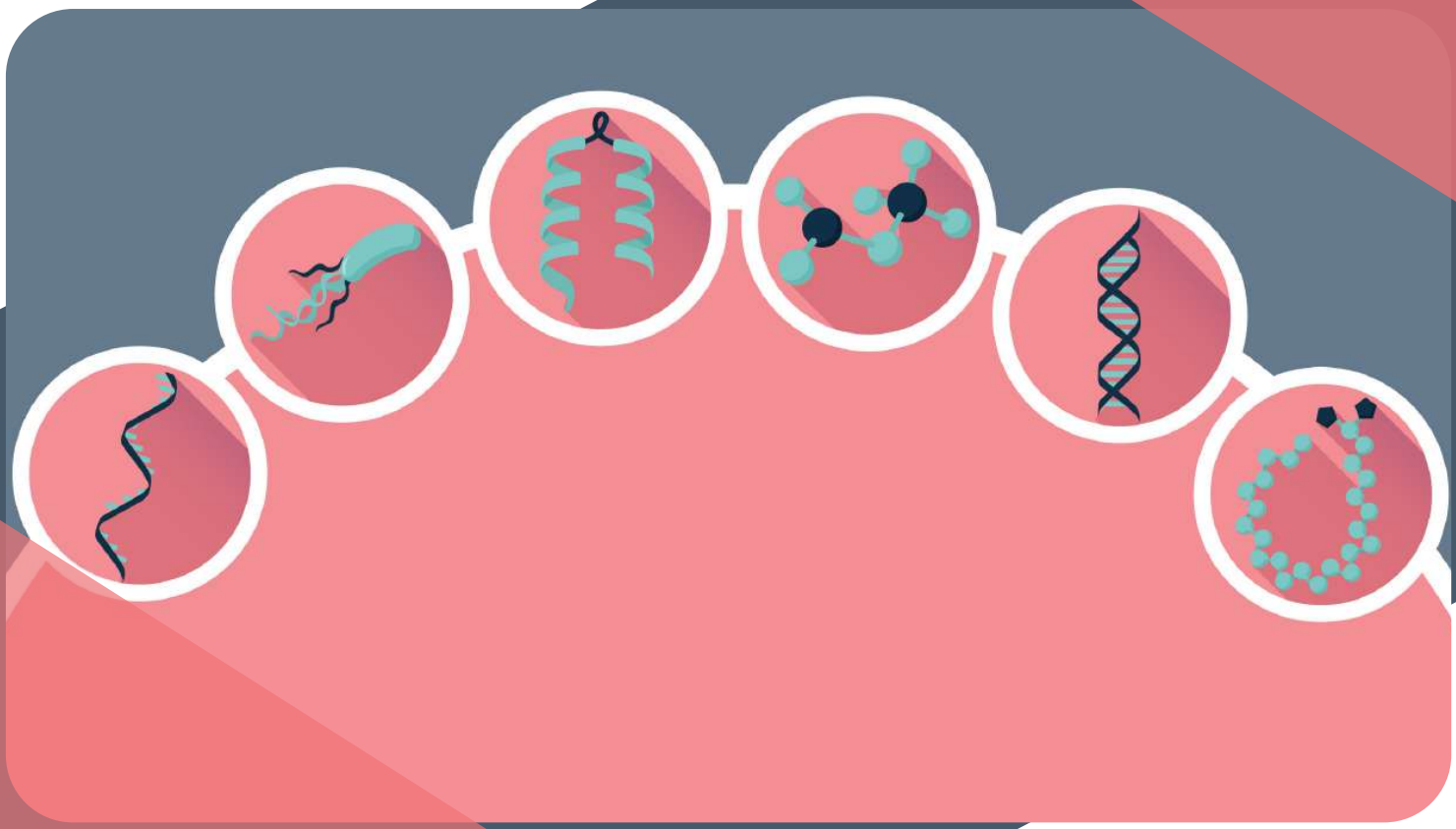
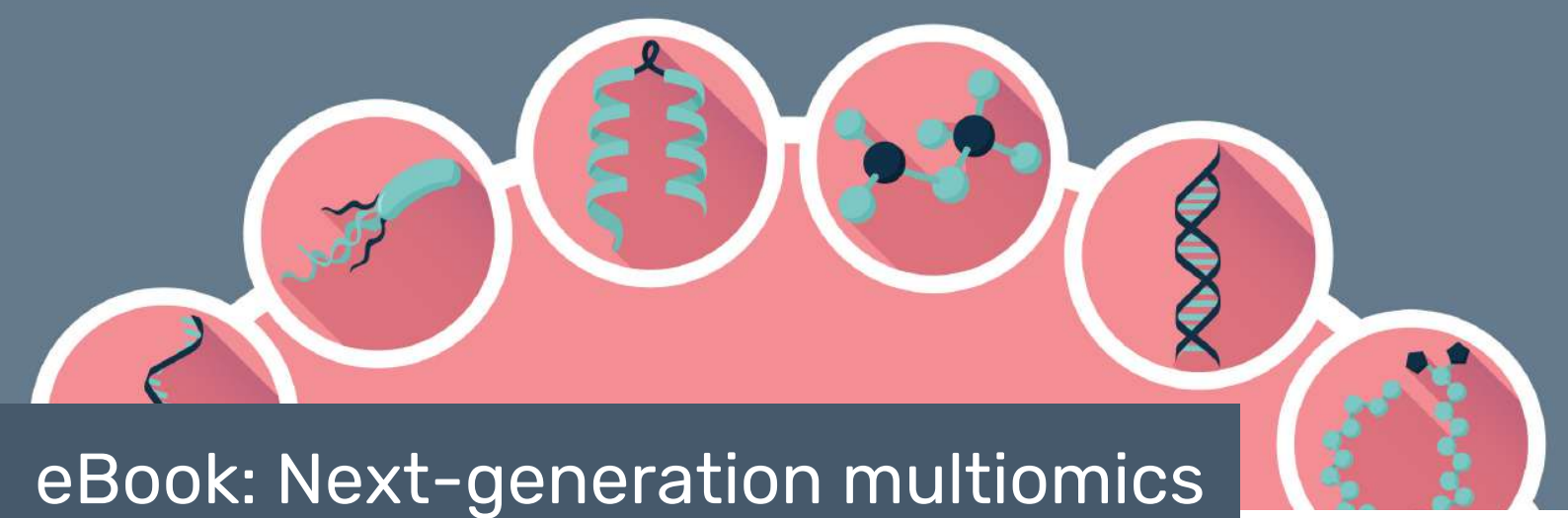
BioTechniques Spotlight



eBook: Next-generation multiomics

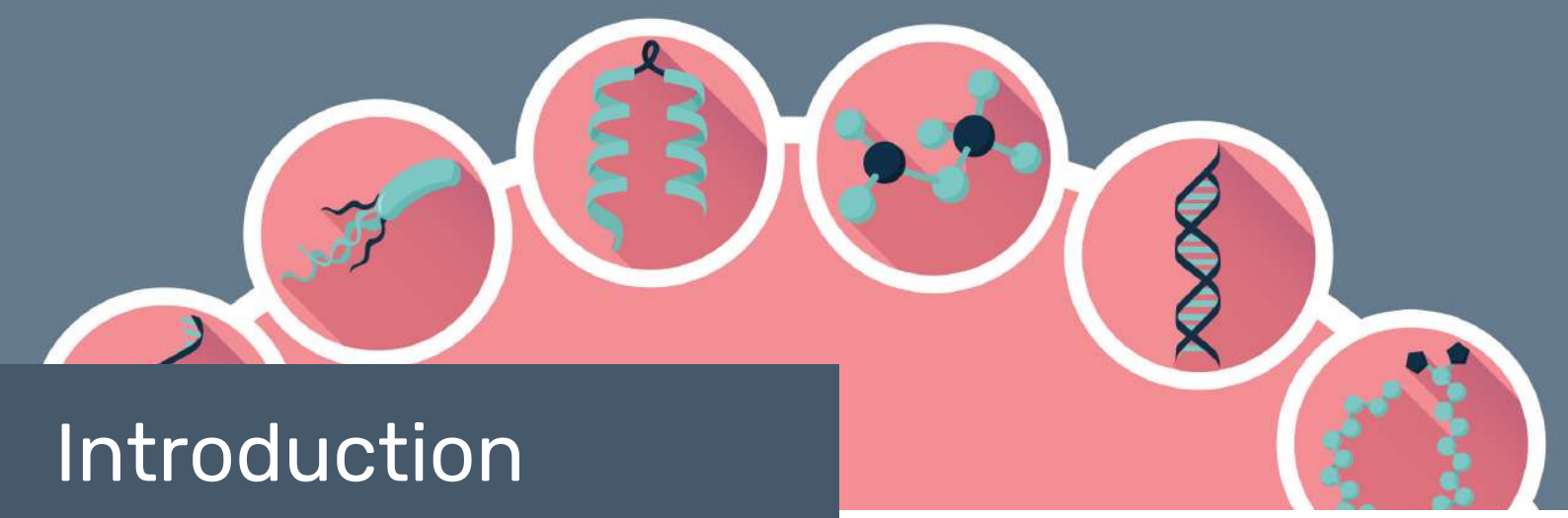
fsg

10x GENOMICS



eBook: Next-generation multiomics

CONTENTS



Introduction

Next-generation multiomics encompasses the increasing trend for multiple readouts from different omic categories to be obtained from a single tissue section or cell, all at the same time. This new wave of multiomic approaches allows researchers to simultaneously explore the genomic, epigenetic, transcriptomic and proteomic profiles of a sample. With these different layers of information available, an unparalleled insight is afforded into the systems and mechanisms operating within specific cells and tissues, providing a greater understanding of cell biology.

Increasingly, these studies are revealing key details about both healthy tissues and complex diseases, such as cancer. Furthermore, the application of next-generation multiomic approaches is expanding from basic disease research into translational research, playing a key role in the identification of novel biomarkers for disease and potential targets for novel therapeutics.

At the core of this frameshift is the development of new single-cell and spatial sequencing technologies, which have allowed researchers to obtain these readouts with increasing specificity and complexity.

In this eBook, you will find updates and expert insights into the latest in the realm of next-generation multiomic techniques and applications. Discover the technologies and tools used in multiomic explorations of basic research and disease discovery and the fascinating insights that have been obtained using these cutting-edge methods. Scan the QR codes throughout the eBook to get access to the full online article.

Tristan Free
Digital Editor,
BioTechniques
tfree@biotechniques.com

INTERVIEW

Designing new tools for multiomic explorations into the human genome

To answer the most perceptive questions, you need the most discerning tools. But when those tools don't exist: what do you do?

Due to their in-depth research into the mechanisms and control of gene expression, members of the Chang Lab at Stanford University (CA, USA) find this conundrum resting itself neatly at their door with increasing frequency. Rather than shoo it away or look for a simpler question to pursue, physician scientist and the lab's PI, Howard Chang welcomes it inside and works with his team to create new methods with which to interrogate the human genome and better understand disease states.

Howard Chang

Here, Chang explains the breadth of multiomic techniques he uses in this research, the diseases that his research could influence and the insight he has gained into cancer, the immunological sex biases that have been laid bare by autoimmune diseases and, more recently, COVID-19. Chang also explains how his initial dermatological training has given him a unique perspective on the future of data interpretation in multiomic studies.

Q) You run a lab at Stanford; what does that lab focus on?

Our lab is comprised of approximately 20 scientists, ranging from postdoctoral fellows to graduate students. We're primarily focused on understanding the hidden information contained in the human genome. Our research programs are based around biologically driven questions, in that they are attempting to understand certain disease states. However, they also have a strong thrust in technology development: a lot of questions we face have no existing techniques that can answer them.

A lot of the method development is done together with my colleague at Stanford, Will Greenleaf. We feel that these two approaches are mutually reinforcing: on many occasions, we have established a new technique and then uncovered new biology.

Q) Are there any multiomic aspects to your studies of the genome?

That is a great question. Our research has always been driven by the principle that we want a comprehensive and unbiased description of the process or the problems that we're dealing with, whether it's the biological process or disease stage. For many years we have focused on genome-scale methods that can cover a biological event. And so many of these techniques turn different kinds of measurements or questions from a biochemical state to a problem that we can solve by leveraging the power and improvements in next-generation sequencing.

Most recently, our interest in gene regulation led us to open chromatin, which is a hallmark of active DNA regulatory elements, to probe the state of gene regulation. Combining studies of chromatin conformation with other modalities: that is where multiomics comes to the fore. This approach allows us to track every step in the lifecycle of gene expression.

Designing new tools for multiomic explorations into the human genome

Q) What specific techniques are you using in these multiomic studies?

We have benefited a lot from understanding gene regulation from the perspective of open chromatin. Several years ago Greenleaf and I introduced ATAC-seq, which is a method that probes open chromatin using a transposase, which is an enzyme that copies and pastes DNA into open chromatin sites exclusively. That method led to the development of single-cell ATAC-seq, with which we can measure open chromatin states in tens of thousands of individual cells. ATAC-seq really improved the speed and scale of measurements compared to other biochemical techniques.

We've subsequently combined single-cell ATAC-seq with single-cell RNA-seq, a method that's also improved in parallel. Those combinations have a lot of advantages. Currently, we are trying to integrate spatial information into our single-cell measurements, in order to simultaneously probe the epitope measurements, using CITE-seq or other related methods.

Q) Are there any particularly interesting insights that you've been able to ascertain using those multiomic approaches?

I would highlight two aspects. One is that these multimodal methods allow us to move from simply observing changes towards understanding mechanisms. We often see in biological states or disease states that gene expression programs are changing, but we don't know why. When we have ATAC-seq, we can see a prior step in the mechanism. It's very important to link these sequential events one to another; simultaneously tracking these different modalities and measurements in the same cell allows you to do that. In some time-course measurements, we can see that the chromatin changes precede the changes in RNA expression. That, of course, is exactly what we expect, but that kind of information gives you more confidence that this is a direct mechanism and that we understand the steps involved.

Several years ago, for example, we studied the process of blood cell development. We could track different changes from hematopoietic stem cells to more restricted types of stem cells that give rise to either white blood cells or myeloid cells. And we could see the changes in chromatin and relate them to the changes in RNA.

A similar kind of phenomenon occurs when we focus on T cells – cells of our immune system that fight infections and cancer. When they're repeatedly stimulated, T cells enter a state called exhaustion. It is an epigenetic state where they become refractory to further stimulation. Again, we can use a multi-modal approach to see the sequential changes in chromatin prior to changes in RNA and prior to changes in the protein markers that we track. Essentially, we can look under the hood and see the driving forces for each of these programs in the cell. That's a good example in tracking changes of cell state and cell fates.

Another interesting way to use multiomics is to gain insights into cell lineage. We've used that approach to study the immune system. Cells in our adaptive immune system, T cells and B cells, undergo something called somatic DNA rearrangement. In this process the immune receptor genes can recombine within the cell, leading to a very large possible repertoire of alterations in the resulting genes – up to

Designing new tools for multiomic explorations into the human genome

10^15 – and those changes are then inherited in all the daughter cells. This provides a trail to track the lineages of immune cell clones as they expand or contract in a disease state.

By combining RNA sequencing of the immune receptor gene loci with chromatin or ATAC-seq and other global RNA changes, we can see at the single-cell level that each of these cells is originally derived from the same lineage. In the context of cancer or cancer immunotherapy, certain clones can no longer react while others take their place and expand in prevalence. Ultimately this allows us to determine which T cells are actually fighting a cancer in the context of cancer immunotherapy.

Q) Do you have any advice for best practices in using these techniques together?

These techniques are potentially complex and each technique has some potential pitfalls. In many cases having a reference point, a biological system where you have some context, is very helpful: just to know that the method is working as expected.

You can make this work with single-cell methods. If the system that you're studying has reference figures derived from bulk measurements, then you can sum the results from your single-cell analyses. This sum should reproduce the bulk measurements as these have essentially come from a collection of single cells. If they do not match, then there's some sort of disconnect or methodological issue.

A few years ago, I and many colleagues in the field put forward a set of standards, which we published in *Nature Biotechnology*, for epigenomic studies.

These include using certain cell lines that are very well characterized to test a new method or process; making sure that they observe what people have seen before in these standard cells. These cell lines are part of the "tier one" of cell lines: they have been extensively studied, distributed to many labs and are a part of the 1000 Genomes Project.

Q) You've highlighted cancer as a disease area that your research could impact. Are there any other diseases that your work could affect?

We're currently excited about some new findings that help explain sex differences in biology and medicine, specifically sex bias in immunity. A major thrust in my work is to generate a personal understanding of gene regulation, with the hope that this would benefit precision medicine.

We know that there are many differences between men and women in the context of immunity. Autoimmune diseases have a very strong bias towards women, four out of five patients with autoimmune diseases are female. In some diseases, like lupus, the ratio is more like nine-to-one female to male. Conversely, in the current COVID-19 pandemic, sex is the third most powerful indicator, after age and learning difficulties, of a negative outcome: men do much worse than women with COVID-19.

Our investigations of the process of X chromosome dosage compensation led us to some recent findings that the mechanism of long-term memory for gene silencing on the X chromosome is potentially more plastic than previously believed, particularly in immune cells. Essentially, this shows that females are different from males because the epigenetic silencing memory system is under continual challenge and it needs continual reinforcement to maintain the status quo.

High-throughput multiomic approaches in the COVID-19 pandemic

In this interview, Rwik Sen (Active Motif, CA, USA) speaks about his recent work published in Future Drug Discovery on the use of metabolomic, proteomic and other approaches to establish processes for diagnosis and therapeutic development for COVID-19.

Rwik Sen

Rwik is a Field Applications Scientist at Active Motif – known for its expertise in epigenetics for over two decades, perfectly aligning with Rwik's interests. He attended Southern Illinois University (IL, USA) for a PhD, and the University of Colorado (CO, USA) for postdoctoral training where he received a fellowship from the American Heart Association. Collectively, Rwik's research on transcription, mRNA biology, DNA repair and craniofacial development, resulted in several peer-reviewed publications and conference presentations with travel awards. ChIP, CRISPR, NGS are among the various tools in his skillset.

Q) Please can you give us a short summary of your article, "High-throughput approaches of diagnosis and therapies for COVID-19: antibody panels, proteomics and metabolomics?"

Various approaches are being pursued worldwide to tackle COVID-19. The review describes the potential of patient-derived antibodies, proteomics and metabolomics profiles in addressing this global health crisis. Research shows that certain antibodies derived and developed from COVID-19 patients can effectively block SARS-CoV-2 infection. Proteomics and metabolomics profiles of patients show abnormal levels of certain entities in our system, which may serve as biomarkers against diseases, and/or become therapeutic targets to attenuate the pathology.

Q) What novel features about SARS-CoV-2 did the proteomic analysis reveal?

A striking novel feature reported by proteomics studies discussed in the review is the identification of two clusters – downregulated proteins and upregulated proteins – in COVID-19 patients. Additional clusters, and the effect of SARS-CoV-2 infection on other properties of protein biology, like turnover and interactions, are also revealed through proteomics studies. Further investigation of the above observations can elucidate how and why the regulation and levels of those proteins are associated with COVID-19, to potentially guide towards therapeutic approaches.

Q) How can metabolomic profiling help to discover new therapeutics for COVID-19?

Metabolomic profiling plays an important role in therapeutic developments against COVID-19. One of the reasons being that certain popular drugs against COVID-19 require intracellular energy to get functionally activated, but studies on many patients show a severe impact on the metabolomic profile which, in turn, will impede the medication. Moreover, studies have diagnosed patients with abnormalities in

High-throughput multiomic approaches in the COVID-19 pandemic

metabolic pathways associated with a variety of biomolecules. Collectively, the above observations associated with metabolomic profiling can significantly help to address the therapeutic challenges associated with COVID-19 and identify novel biomarkers.

Q) How can these techniques be used to prevent any future pandemics?

Time is of the essence when battling a global pandemic. Achievements associated with COVID-19 research are expected to serve as extremely beneficial platforms against future pandemics to a certain extent. Although there are differences between various pathogens, which can potentially cause pandemics, the scientific truth remains constant. Technology that is engineered now can be developed according to the specific needs of the future. Hence, the collective tools that have shown promise against COVID-19, within and beyond the purview of this review, will likely serve as great resources for future research by considerably minimizing the time to establish new foundations.

Q) How has the pandemic impacted the field over the past year?

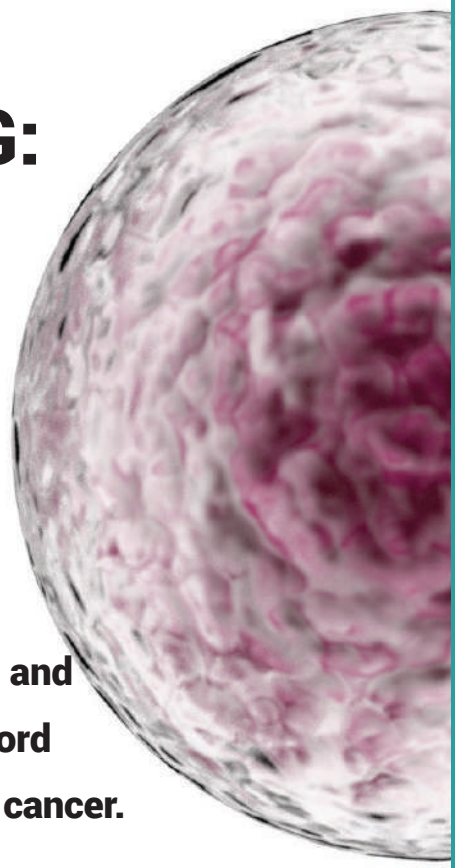
The pandemic has exerted a multifarious impact on the field in ways that are yet to be discovered. So far, almost all known disciplines of health have shown some impact of the pandemic in varying degrees. Apart from the severe effects on the immune system and multi-organ failures, the impact has been detected in epigenetic, proteomic and metabolomic profiles. Hence, we need to understand if those effects are harbingers of maladies in future generations resulting from COVID-19 patients. The field has been impacted by the development of various therapeutic and diagnostic approaches, e.g., different kinds of vaccines, antibody-based therapies, high-throughput omics profiling, etc.

Q) Any final comments?

Although several challenges persist, and caution is needed to avoid future outbreaks, the world acknowledges and thanks all medical and non-medical frontline and emergency workers, scientific researchers and sponsors. It is extremely sad when we think about all the lives lost. It can be hoped that the scientific progress during these difficult times will help to prevent such losses in the future through the development of vaccines, therapies, diagnostic tools, personalized medicine involving the analysis of high-throughput multiomics datasets, etc. Care needs to be taken to make medical resources accessible to vulnerable populations, and generally all across the globe.

BioTechniques
The International Journal of Life Science Methods

SINGLE-CELL SEQUENCING: THE TECHNOLOGICAL REVOLUTION BEHIND A NEW WAVE OF MULTIOMIC STUDIES IN BASIC AND CANCER RESEARCH



Amidst the development of new single-cell technologies and the implementation of multiomic approaches, two Stanford labs are spearheading a new field of research to combat cancer.

Since single-cell sequencing featured as Nature's Method of the Year for 2013, the technology has seen an exponential rise in prevalence. In 2013, a search for 'single-cell sequencing' on PubMed would have returned 373 papers published that year; a search today shows that over 2500 papers mentioning the term have already been listed on the site in 2021, with this year now set to overtake the 2799 recorded in 2020. The rise of single-cell techniques has triggered the evolution of a new approach to research – multiomics – which has risen from relative obscurity in 2013 when only 59 publications mentioned the keyword, to now account for over 1400 results to date in 2021, again surpassing the previous year's total.

While this correlation has been rudimentarily established, it serves to highlight the growing list of capabilities that single-cell technologies have offered to researchers, enabling them to tackle longstanding problems in numerous fields with new, multiomic approaches.

Two factors in the development of single-cell technologies have contributed to this increase. The increasing abundance of techniques available that cover different omic modalities – from chromatin availability and DNA methylation to DNA and RNA sequences – has widened the amount of information that can be obtained from a single cell. Additionally, the increasing trend for combining these techniques into one has allowed for these different layers of omic information to be collected simultaneously. For instance, scNMT-seq captures gene expression, DNA methylation and chromatin accessibility information from a single sample [1]. What's more, as individual techniques become more sophisticated, they also become more compatible, allowing multiple techniques to examine a single cell in parallel.

It is the ability to simultaneously collect this information that has characterized the next generation of multiomic studies, uprooting new fields of study and revealing novel insights into disease pathology and targets for drug development.

THE REGULOME: A NEW REALM FOR A NEW APPROACH

At the helm of one such emerging field are two labs at Stanford University (CA, USA) – the Greenleaf and Chang Labs are headed up by Will Greenleaf and Howard Chang, respectively. Speaking with Greenleaf is an invigorating experience. Not only due to the passion for his research that streams from every aspect of his speech – his excited alto, dramatic vocabulary, fascinating tangents and engaging metaphors – but for his exploration of the burgeoning field of research that he calls the regulome.

The regulome refers to the collection of physical molecular components that control gene expression through factors such as chromatin accessibility and regulate the expression programs that define a cell. Speaking to BioTechniques on this topic in a recent Talking Techniques episode, Greenleaf revealed how the advance of single-cell techniques and the rise of multiomics have been essential in the development of this field [2].

"This [investigating the regulome] tends to mean converting protein–DNA/RNA interactions into something that can be sequenced using high-throughput sequencers." To capture all the layers of information required to examine the regulome, several techniques are required. Among others, Greenleaf deploys single-cell RNA and protein ▶

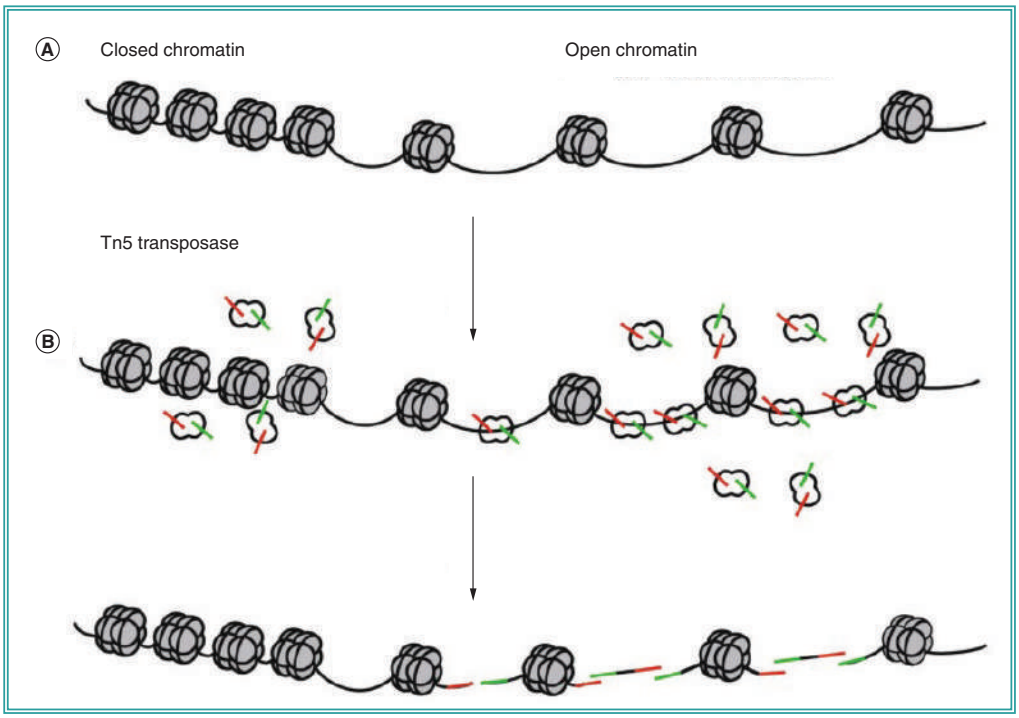


Figure 1. A schematic of the ATAC-seq working principle. Reprinted with permission from [4]. Published under CC BY.

sequencing technologies to identify 'what' is happening within a cell at a given time. To understand 'why' these things are happening, he interrogates the epigenome, primarily with a technique named ATAC-seq.

This technique was developed by Jason Buenrostro (Harvard University, MA, USA) under Greenleaf and Chang's supervision back in 2013 [3], and uses a transposase to map regions of open chromatin in a compacted genome (Figure 1, [4]). While describing the development of ATAC-seq, Greenleaf highlighted the importance of adapting the method to function on single cells, hence avoiding the *"dreaded ensemble average"* of a homogenized complex sample:

"The analogy I use [to highlight the value of single-cell studies] is that if a boat is traveling from the east to the west of the USA you can either go through the Panama Canal or you can go around the tip of South America. The ensemble average goes right through Brazil; no boat takes that route. If you average things together, you can get really misleading information."

Greenleaf's interest in the regulome hinges on his fascination with how cells differentiate into each developmental state and how stable each of these changes are. By using a single-cell multiomic approach, he is able to observe changes in the chromosome availability, followed by variations in gene expression and protein abundance at various time points. This provides a complete omic pathway of the changes occurring in a cell that lead to differentiation. This basic understanding, he believes, can be used to help us identify the malignant changes and variations in regulatory programs that lead cells to differentiate into cancerous cells.

FROM NEW FIELDS TO OLD FOES

Almost any new technology that provides an additional insight or level of detail compared to its predecessors is turned to tackle cancer. With the heterogeneity of cancer cells well established, both between individuals and within the same tumor, it is no surprise that single-cell techniques have been embraced within cancer research in an attempt to once again avoid the dreaded ensemble average.

In a series of papers since 2016, Greenleaf and Chang have used the tools developed in their respective labs to gain a further understanding of leukemia and how to improve potential cancer therapeutic approaches. In the first of these papers [5], the research team used an ATAC-seq protocol optimized for the analysis of blood cells, Fast-ATAC-seq, and RNA-seq to examine the chromatin accessibility and transcriptional landscape in the cells of 137 blood samples from nine healthy controls and 12 acute myeloid leukemia (AML) patients.

This study successfully developed an epigenetic and transcriptomic reference atlas of the 16 different blood cell types with a greater identifying value placed on the epigenetic aspect of the atlas. The atlas was capable of defining each cell type and identifying a cell's developmental trajectory. Furthermore, the researchers were able to identify the regulators directing normal hematopoiesis before using scATAC-seq to decipher the cancer-specific deviations from the regulatory norm.

In an update to this study, Greenleaf and Chang revisited the regulatory landscape of leukemia, broadening the focus to mixed-phenotype acute leukemia (MPAL) [6]. To do this, the team designed a single-cell framework enabling protein quantification, transcriptome and chromatin accessibility analysis. At the core of this framework were two 10x Genomics' (CA, USA) single-cell sequencing tools: droplet scATAC-seq and CITE-seq, which provide both gene expression and protein abundance data at a single-cell level [1].

Initially applying this framework to bone marrow and peripheral blood mononuclear cells, the team established maps

of immunophenotypic, transcriptomic and epigenetic blood development before confirming a healthy epigenetic baseline for hematopoiesis. Despite the high degree of heterogeneity in the cancers observed, these maps enabled the team to identify common malignant signatures and transcription factors (TFs) that regulate these signatures. In particular, a potential oncogene – the TF RUNX1 – was noted as a regulator of malignant genes associated with poor survival in MPAL, highlighting the value of this approach in identifying novel therapeutic targets [6] for cancers.

Since this publication, several others have been released using multiomic single-cell technologies to explore heterogeneity in lung cancers and to establish common oncogenic regulatory factors behind these cancers [7,8]. Among the numerous other cell studies using these techniques in the cancer research space, the exploration of the relationship between tumors and T cells has featured frequently [9,10].

INVESTIGATING THE BASIC TO IMPROVE THE THERAPEUTIC

Another rising trend in cancer research is the development of immunotherapies, in part driven by the improvement of gene-editing technologies, such as CRISPR, which are readily available to the community. However, a current roadblock in the path of these therapeutics is the development of T-cell exhaustion and dysfunction in the tumor microenvironment [11]. This exhaustion prevents T cells from proliferating effectively and reduces the release of anti-tumor effector molecules, enabling tumor cells to grow and proliferate unchecked [11].

Focusing on the plight of T-cell exhaustion in CAR-T therapies, Chang and Greenleaf set out to establish the regulatory networks involved in the development and maintenance of the exhausted cell state [12]. The fact that chromatin accessibility plays a role in this development had been previously established, but the mechanistic details of this association had yet to be established.

In a previous study, the team had identified that CD19-28Z-CAR-T cells resist exhaustion better than their GD2-targeting counterparts, HA-28z-CAR-T cells, using scRNA-seq to determine differences in the expression of inhibitory receptors, effector molecules and AP-1 family TFs versus memory state associated genes [13]. Building on this, the team used ATAC-seq in these two cell types to identify the differences in chromatin accessibility at different time points during a 14-day *in vivo* maturation.

The team combined this approach with further examinations of the differential transcriptome and enhancer-connectome profiles. This allowed them to identify differences in the chromatin structure of exhaustion-prone cells, revealing greater accessibility of sites proximal to exhaustion-associated genes such as PDCD1. Many of these sites were also found to be enriched with the AP-1 TF motifs, allowing increased binding of this TF, which is known to promote exhaustion in CAR-T cells [13], to the DNA [12]. The transcriptome profiles revealed increased expression of these exhaustion-associated genes following the epigenetic changes.

The study was also able to reveal that the chromatin accessibility landscape of exhausted T cells was differential between mice and humans, highlighting the limitations of mouse model studies in this area [12].

To highlight the translational value of the study, the team used CRISPR technology to excise the regulatory elements of the genome that they had identified as controlling expression of PDCD1, successfully reducing the expression of PD-1 [12]. This represents a significant step toward limiting T-cell exhaustion for CAR-T therapeutics and highlights a new set of targets for gene-editing technologies in the improvement of immunotherapies.

THE CRITICAL QUALITIES OF CREATIVITY AND COLLABORATION

This article highlights the dramatic impact that single-cell technologies and multiomics have had on researchers from one university, in one aspect of basic and disease research. But these technologies and approaches have fueled the fire of enough labs and fields to fill several articles, telling a variety of stories with different protagonists.

Consider the impact of these studies during the COVID-19 pandemic in improving our understanding of therapeutic target identification [14] and varying immune responses [15]. Greenleaf has also contributed to this space with a recent study that exposed the widespread dysfunction of the peripheral innate immunity in severe and fatal COVID-19 [16]. The paper also highlighted the chromatin accessibility differences at key TF binding sites for cytokine genes, potentially explaining the lack of monocytic cytokine production frequently observed in fatal COVID-19.

Alternatively, turn to the phenomenal impact observed in neuroscience, providing an unparalleled insight into the wide variety of cell types and their differences and laying the groundwork for new insights into Alzheimer's disease [17] and autism spectrum disorder studies [18].

Among the new technologies touted on the horizon, some look to improve chromatin accessibility assays to provide an insight into which regions of open chromatin are bound by which TFs at a specific time point. These technologies are being designed to use methyltransferase *"as a spray paint,"* in Greenleaf's words [2], providing yet another layer of information to be obtained from cells.

Needless to say, as these technologies continue to proliferate and become more sophisticated, the breadth of the network of fields and researchers applying them will continue to increase. Only the significance of these future applications is yet to be guaranteed. For that, we trust that there are many creative labs like Chang and Greenleaf's in universities worldwide, keen to collaborate and create with their colleagues, with a voracious appetite to approach established issues with new technologies.

Written by Tristan Free

REFERENCES

1. Perkel J. Single-cell analysis enters the multiomics age. *Nature* 595, 614–616 (2021).
2. *BioTechniques*. Talking Techniques. Revealing the regulome: using multiomic approaches to explore epigenetics and DNA expression. www.biotechniques.com/podcasts/10x_mosptl_talking-techniques-revealing-the-regulome-using-multiomic-approaches-to-explore-epigenetics-and-dna-expression/
3. Buenrostro J, Giresi P, Zaba L, Chang H, Greenleaf W. Transposition of native chromatin for fast and sensitive epigenomic profiling of open chromatin, DNA-binding proteins and nucleosome position. *Nat. Methods* 10, 1213–1218 (2013).
4. Sun Y, Miao N, Sun T. Detect accessible chromatin using ATAC-sequencing, from principle to applications. *Hereditas* 156, 29 (2019). hereditasjournal.biomedcentral.com/articles/10.1186/s41065-019-0105-9
5. Corces M, Buenrostro J, Wu B *et al.* Lineage-specific and single cell chromatin accessibility charts human hematopoiesis and leukemia evolution. *Nat. Genet.* 48(10), 1193–1203 (2016).
6. Granja J, Klemm S, McGinnis L *et al.* Single-cell multiomic analysis identifies regulatory programs in mixed-phenotype acute leukemia. *Nat. Biotechnol.* 37(12), 1458–1465 (2019).
7. Laughney A, Hu J, Campbell N *et al.* Regenerative lineages and immune-mediated pruning in lung cancer metastasis. *Nat. Med.* 26, 259–269 (2020).
8. Marjanovic N, Hofree M, Chan J *et al.* Emergence of a high-plasticity cell state during lung cancer evolution. *Cancer Cell.* 38(11), 229-246 (2020).
9. Yost k, Satpathy A, Wells D *et al.* Clonal replacement of tumor-specific T cells following PD-1 blockade. *Nat. Med.* 25, 1251–1259 (2019).
10. Li A, Herbst R, Canner D *et al.* IL-33 signaling alters regulatory T cell diversity in support of tumor development. *Cell Rep.* 29, 2998–3008 (2019).
11. Zhang Z, Lui S, Zhang B *et al.* T cell dysfunction and exhaustion in cancer. *Front. Cell Dev. Biol.* 8, 17 (2020).
12. Gennert D, Lynn R, Granja J *et al.* Dynamic chromatin regulatory landscape of human CAR T cell exhaustion. *Proc. Natl Acad. Sci. USA* 118(30), e2104758118 (2021).
13. Lynn R, Weber E Sotillo E *et al.* c-Jun overexpression in CAR T cells induces exhaustion resistance. *Nature* 576(7786), 293–300 (2019).
14. Singh R, Singh P, Kumar R *et al.* Multi-omics approach in the identification of potential therapeutic biomolecule for COVID-19. *Front. Pharmacol.* 12, 652335 (2021).
15. Stephenson E, Reynolds G, Botting R *et al.* Single-cell multi-omics analysis of the immune response in COVID-19. *Nat. Med.* 27, 904–916 (2021).
16. Wilk A, Lee M, Wei B *et al.* Multi-omic profiling reveals widespread dysregulation of innate immunity and hematopoiesis in COVID-19. *J. Exp. Med.* 218(8), e20210582 (2021).
17. Jiang J, Wang C, Qi R *et al.* scREAD: a single-cell RNA-seq database for Alzheimer's disease. *iScience* 23(11), 101769 (2020).
18. Trevino A, Muller F, Andersen J *et al.* Chromatin and gene-regulatory dynamics of the developing human cerebral cortex at single-cell resolution. *Cell* doi:10.1016/j.cell.2021.07.039 (2021) (Epub ahead of print).

Multiomic insights to advance human health

Introduction

As we enter a century where transformative advances in biology and medicine will reshape the way we deliver human health, researchers need approaches that can keep up with the fast pace of their science. From gene expression to chromatin accessibility, T-cell receptor/B-cell receptor (TCR/BCR) typing, and protein expression, single cell and spatial solutions enable researchers to gain multiomic insights that drive the leading edge of what's possible. Browse the collection of publications below to see how researchers are using 10x Genomics technology for multiomic characterization of complex human biology.

Single cell and spatial gene expression

Featured publication	Experiment snapshot	Research highlights
Integrating Microarray-Based Spatial Transcriptomics and Single-Cell Rna-Seq Reveals Tissue Architecture in Pancreatic Ductal Adenocarcinomas R Moncada et al., *Nat Biotechnol* (2020).	**Research area**: Oncology **10x Genomics products**: Spatial Transcriptomics (now available as Visium Spatial Gene Expression) **Sample type**: Primary human pancreatic ductal adenocarcinomas	Integrated single cell RNA sequencing (scRNA-seq) with spatial gene expression profiling to characterize cell types and subpopulations within pancreatic tumors, and annotated spatially restricted enrichments and other distinct coenrichments. Identified colocalization of cancer cells expressing a stress-response gene module and inflammatory fibroblasts that produce IL-6. This cytokine participates in signaling cascades with factors encoded by the same stress-response genes identified in local cancer cells, suggesting a link between the stress-response cancer cell state and inflammatory cell types in the microenvironment.
Multimodal Analysis of Composition and Spatial Architecture in Human Squamous Cell Carcinoma AL Ji et al., *Cell.* (2020)	**Research area**: Oncology **10x Genomics products**: Chromium Single Cell Gene Expression and Visium Spatial Gene Expression **Sample type**: Human cutaneous squamous cell carcinoma (cSCC) tumors paired with normal tissue	Constructed a single cell transcriptomic atlas of cell subpopulations within cSCC, identifying a population of tumor-specific keratinocytes (TSKs). Spatial transcriptomic analysis localized the TSKs to a specific niche at leading edges of the tumor, while CRISPR screens identified a TSK-specific gene network containing genes associated with the enhancement of cell migration and stromal invasion. Results suggest further investigation into this gene network may provide new therapeutic targets and begin to inform the clinical management of carcinomas. Patients with a high expression of TSK markers exhibited significantly lower progression-free survival after treatment with PD-1 checkpoint inhibitors.

Featured publication	Experiment snapshot	Research highlights
A Spatiotemporal Organ-Wide Gene Expression and Cell Atlas of the Developing Human Heart M Asp et al., *Cell.* (2020)	**Research area:** Developmental Biology **10x Genomics products:** Chromium Single Cell Gene Expression and Spatial Transcriptomics (now available as Visium Spatial Gene Expression) **Sample type:** Human heart tissue	Combined single cell and spatial gene expression to map cell type–specific gene expression to specific anatomical domains during three developmental stages of human cardiogenesis. Layered on targeted In Situ Sequencing (ISS) to refine the spatiotemporal gene expression map with subcellular resolution. This multomic approach enables researchers to explore global spatial transcriptional patterns in tissues, deconvolve their cellular heterogeneity, and selectively target key genes with spatially heterogeneous expression patterns that are responsible for cell-type difference. Created a publicly available web resource of the human developing heart to help facilitate future studies.

Single cell gene expression and chromatin accessibility

Featured publication	Experiment snapshot	Research highlights
Mouse Models of Neutropenia Reveal Progenitor-Stage-Specific Defects DE Muench et al., *Nature.* (2020)	**Research area:** Genetic Disease **10x Genomics products:** Chromium Single Cell Gene Expression and Chromium Single Cell ATAC (Assay for Transposase Accessible Chromatin) **Sample type:** Bone marrow and peripheral blood from mouse models of human severe congenital neutropenia (SCN) with patient-derived mutations in the GFI1 transcription factor	Determined the effects of SCN mutations by generating single cell references for granulopoietic genomic states with linked epitopes, aligning mutant cells to their wild-type equivalents and identifying differentially expressed genes and epigenetic loci. Discovered that GFI1-target genes are altered sequentially, as cells go through successive states of differentiation. These insights facilitated the genetic rescue of granulocytic specification but not post-commitment defects. Demonstrated a transferable workflow that can be harnessed to answer developmental questions across disciplines. The results suggest that such analyses can reveal cell state–specific effects of mutations with direct consequences for attempts to repair defects.
Single-Cell Multiomic Analysis Identifies Regulatory Programs in Mixed-Phenotype Acute Leukemia JM Granja et al., *Nat Biotechnol.* (2019).	**Research area:** Oncology **10x Genomics products:** Chromium Single Cell Gene Expression and Chromium Single Cell ATAC **Sample type:** Healthy human PBMCs, BMMCs, and CD34^{+} bone marrow cells; Human peripheral blood and bone marrow aspirate from leukemia patients	Integrated single cell transcriptome profiling, chromatin accessibility, and protein quantification analysis to study the epigenomic landscape of healthy blood development compared to blood from patients with mixed-phenotype acute leukemia. Identified common malignant signatures across patients as well as patient-specific regulatory features that are shared across phenotypic compartments of individual patients. Demonstrated the utility of integrated, single multiomic analysis to identify the differentiation status of tumors and pathogenic cellular subtypes with possible future application in identifying personalized therapeutic targets.

Featured publication	Experiment snapshot	Research highlights
Hic1 Defines Quiescent Mesenchymal Progenitor Subpopulations with Distinct Functions and Fates in Skeletal Muscle Regeneration RW Scott et al., *Cell Stem Cell.* (2019).	**Research area:** Developmental Biology **10x Genomics products:** Chromium Single Cell Gene Expression and Chromium Single Cell ATAC **Sample type:** Mouse muscle tissue	Identified Hypermethylated in cancer 1 (Hic1) as a marker of tissue-resident mesenchymal progenitors (MPs) in skeletal muscle. Integrated scRNA-seq and single cell ATAC sequencing (scATAC-seq) analysis identified multiple MP subpopulations, which further analyses showed to have distinct functions and lineage potential. Demonstrated that Hic1 regulates MP quiescence and identifies MP subpopulations with transient and enduring roles in muscle regeneration.

Single cell immune profiling for COVID-19 research

Featured publication	Experiment snapshot	Research highlights
Single-Cell Landscape of Immunological Responses in Patients with Covid-19 JY Zhang et al., *Nat Immunol.* (2020).	**Research area:** Infectious Disease / Immunology **10x Genomics products:** Chromium Single Cell Immune Profiling (Gene expression and TCR/BCR sequencing) **Sample type:** Human PBMCs	Combined scRNA-seq and TCR/BCR sequencing to analyze the functional properties of immune cells in COVID-19 patients with mild, moderate, and severe cases, and in healthy donors. Revealed dynamic immune responses during disease progression with severe cases hallmarked by dysregulated interferon response and profound immune exhaustion with skewed T-cell receptor repertoire and broad T-cell expansion. Demonstrates the utility of combined transcriptomic and immune receptor typing for characterization of the complex, dynamic immune responses to infectious disease.
A Human Circulating Immune Cell Landscape in Aging and Covid-19 Y Zheng et al., *Protein Cell.* (2020).	**Research area:** Infectious Disease / Immunology **10x Genomics products:** Chromium Single Cell Immune Profiling (Gene expression and TCR/BCR sequencing) and Chromium Single Cell ATAC **Sample type:** Human PBMCs	Combined scRNA-seq, mass cytometry, and scATAC-seq to compare immune cell types in young and old adults, including two cohorts of incipient and recovered COVID-19 patients. Found that SARS-CoV-2 infection caused different immune cell landscape changes in aged and young adult patients, and further increased age-induced immune cell polarization and upregulation of inflammatory genes. Provides comprehensive characterization of immune landscape in young and aged adults after SARS-CoV-2 infection.

Contact us
10xgenomics.com | info@10xgenomics.com

© 2020 10x Genomics, Inc. FOR RESEARCH USE ONLY. NOT FOR USE IN DIAGNOSTIC PROCEDURES.

Identification of a tumor–specific gene regulatory network in human B-cell lymphoma

Introduction

Simultaneous readout of transcriptomic and epigenomic data from the same cell at single cell resolution allows for direct reconstruction of cell type–specific gene regulatory networks that does not rely on inference or assumptions to tie the two data types together. Here, we show how multiomic analysis of paired RNA-seq and ATAC-seq data from the same single cells using Chromium Single Cell Multiome ATAC + Gene Expression enables direct linkage of differentially accessible DNA regions to proximal differentially expressed genes to identify putative regulatory targets. As a result, you can answer questions not only about what genes are expressed in a single cell, but how expression is regulated through associated open chromatin regions. In a diffuse small B-cell lymphoma sample, we confirmed Paired Box 5 (PAX5) as an important regulator in tumor B cells and identified a network of potential PAX5 target genes.

Highlights

- Distinguish tumor versus normal cells in a heterogeneous sample
- Reconstruct cell type–specific gene regulatory network
- Confirm PAX5 as a critical regulator specific to tumor B cells
- Identify putative target genes downstream of PAX5

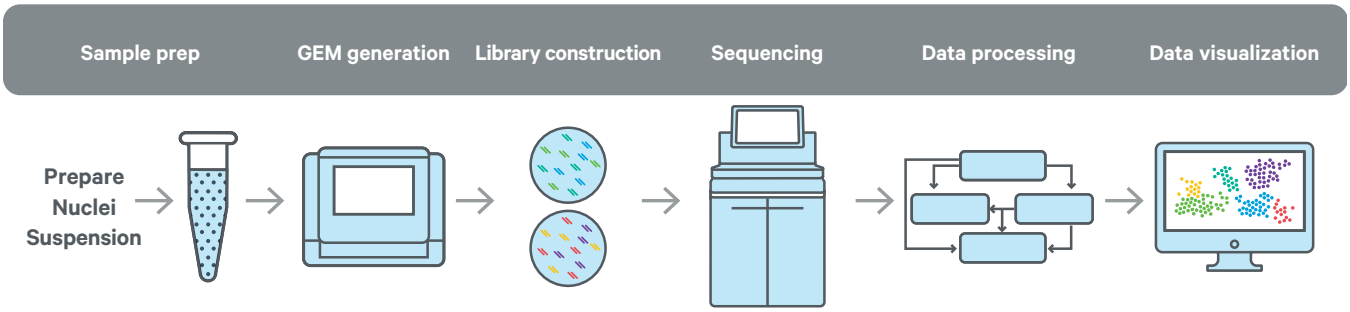


Figure 1. Experimental methods for nuclei isolation and multiomic data generation. Flash-frozen intra-abdominal lymph node tumor, with pathologist annotation of diffuse small B-cell lymphoma tissue, was acquired from BioIVT Asterand®. Nuclei were isolated following the Nuclei Isolation from Complex Tissues for Single Cell Multiome ATAC + Gene Expression Sequencing Demonstrated Protocol (CG000375). Isolated nuclei were flow sorted before permeabilization. Nuclei were transposed in bulk before single nuclei encapsulation in GEMs (Gel Bead-in-emulsion), where DNA fragments and the 3' ends of mRNA were barcoded. Paired ATAC and gene expression libraries were generated from 14,000 total nuclei as described in the Chromium Next GEM Single Cell Multiome ATAC + Gene Expression User Guide (CG000338 Rev A) and sequenced on an Illumina NovaSeq™ 6000 v1.5.

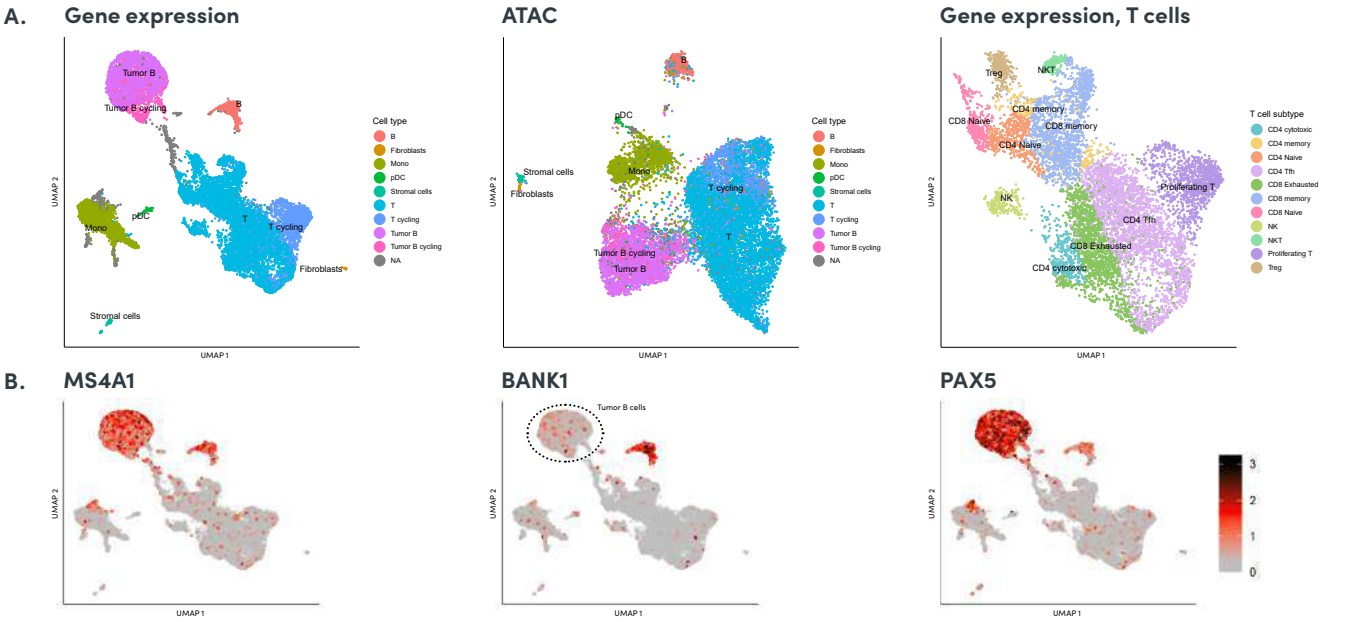


Figure 2. Simultaneous measurement of gene expression and open chromatin profiles from the same single nuclei enables clustering based on either modality. A. Shown are clustering and manual annotation based on gene expression for all 14,000 nuclei (left); gene expression-derived annotations layered on ATAC projections (middle); and the gene expression plot on the left restricted to the T-cell populations (right). **B.** Highlighted are expression levels of select genes, including *MS4A1*, a canonical B-cell marker (left); *BANK1*, an attenuator of BCR activation pathway that is repressed in tumor cells relative to normal B cells (middle); and *PAX5*, required for B-cell differentiation (right).

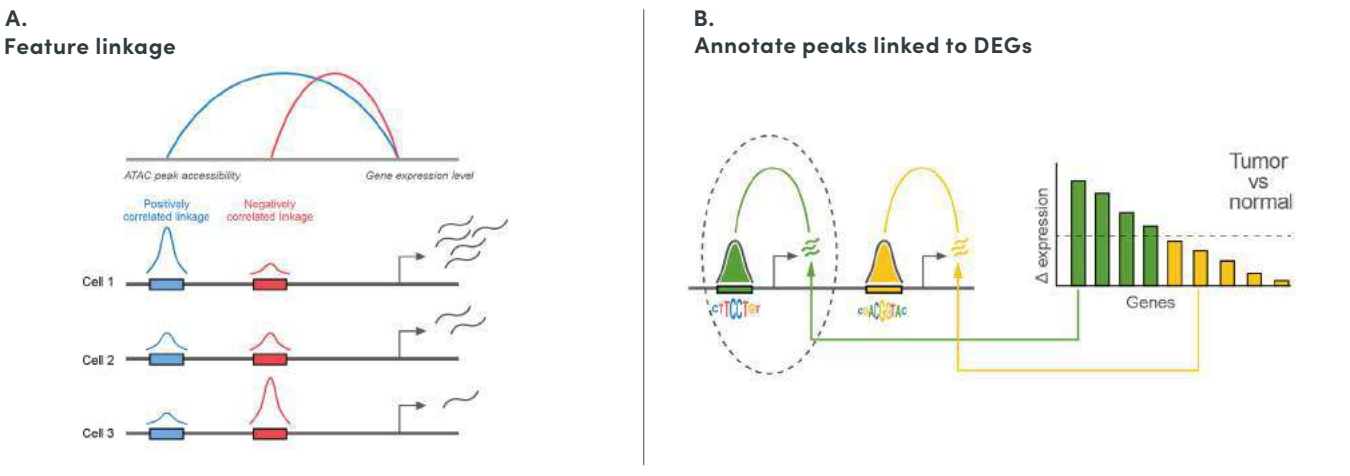


Figure 3. Computational strategy for identification of cell type–specific gene regulatory networks. A. In 10x Genomics Cell Ranger ARC software, feature linkages are defined as pairs of genomic features, such as peaks and genes, that exhibit significant correlation in their chromatin accessibility and transcript level, respectively, across cells. Feature linkages can be positively or negatively correlated. For example, an open enhancer region may have a positive correlation with gene expression of its associated transcript (blue), while the binding of a repressor would result in a negatively correlated feature linkage (red). The greater the correlation between open chromatin signal and gene expression, the taller the arc. **B.** To identify a gene regulatory network in tumor B cells, genes were first filtered based on significant transcriptional upregulation in tumor B cells relative to normal B cells ($p < 10^{-20}$), resulting in 198 differentially expressed genes (DEGs, green). Peaks associated with DEGs (green) were identified using feature linkages. Tumor B cell–specific enriched motifs were then identified using DEG-linked peaks. Enriched motifs and linked upregulated genes were used to define a B cell lymphoma–specific gene regulatory network (Figure 4).

What to look for

Since mRNA and ATAC data are generated from the same cells, cell-type annotations can be transferred from one modality to the other (Figure 2A, middle). In addition to the identification of B cells, monocytes, and T-cell subtypes using canonical cell markers like the B-cell marker *MS4A1*, tumor B cells were distinguishable from normal B cells based on upregulated *CD40* expression (data not shown) and reduced *BANK1* (Figure 2B). *PAX5* was significantly upregulated in tumor B cells relative to normal B cells (Figure 2B), and has previously been identified as a core regulator of chronic lymphocytic leukemia (CLL) (Ott et al., 2018).

Paired gene expression and open chromatin signals pave the way for high-confidence gene regulatory network predictions using feature linkages, which are calculated automatically in Cell Ranger ARC (Figure 3A). Feature linkages help build putative gene regulatory networks by providing correlated gene expression and open chromatin regions across the genome. To identify tumor B cell–specific gene regulatory networks, we first annotated feature linkages by genes upregulated in tumor B cells to identify peaks that were potential drivers of differential expression. We then identified motifs enriched in these peaks relative to a set of matched background motifs within tumor B cells (Figure 3B). Using this method, we found that the PAX1 motif was the most enriched (Figure 4).

PAX1 and PAX5 motifs are highly similar, however *PAX1* is not expressed in tumor B cells, while *PAX5* is highly expressed (Figure 4). Therefore, it is likely the PAX5 transcription factor is binding the identified PAX1 motif. This inference is only possible with paired gene expression and open chromatin information from the same cells.

To understand the role of PAX5 in tumor B cells, we zoomed in on the *PAX5* locus, which is differentially expressed between B cells and tumor B cells (Figure 5). Expression of *PAX5* is highly correlated with open PAX5 motif sites in a previously identified super-enhancer, suggesting autoregulation (Figure 5, dashed box). Additional feature linkages contribute further to the reconstruction of a putative tumor B cell–specific gene regulatory network, and suggest PAX5 may also regulate the immune transcription factor genes *NFATC1, TCF4, IKZF1*, and *IRF8* (Figure 4). The importance of PAX5 and its position as a key genetic regulator in tumor B cells is consistent with previously published results showing that, of 147 transcription factors tested, loss of PAX5 had the greatest effect on cell proliferation in a CLL cell line (Ott et al., 2018). While confirmation of individual links in our predicted gene regulatory network requires functional tests, the confidence in regulatory connections is greatly increased by joint measurement of mRNA and ATAC data.

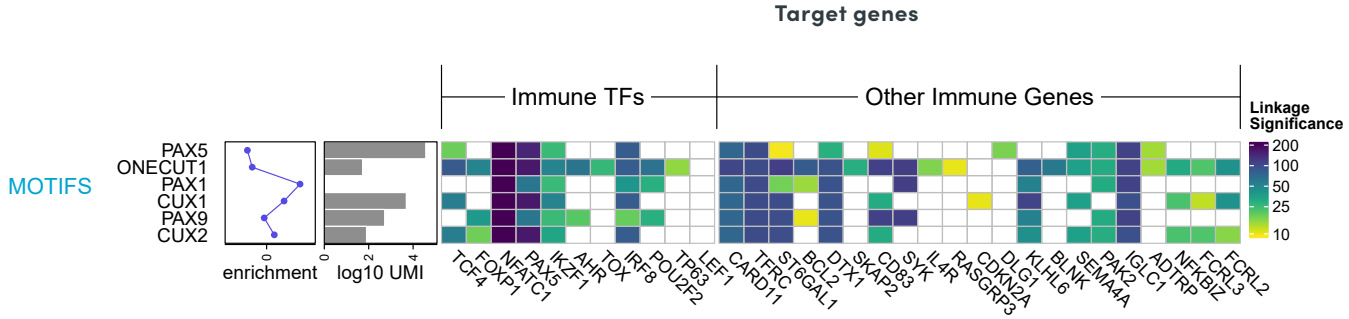


Figure 4. Feature linkages help build a tumor-specific gene regulatory network. The table summarizes significant feature linkages between motifs in the PAX/CUX/ONECUT family and a selection of immune-related transcription factors (TFs) and other immune genes that are differentially expressed in tumor B cells. At far left, the blue line plot shows motif enrichment scores, calculated using the analysis outlined in Figure 3. Gene expression levels of the transcription factors expected to bind each motif are indicated in the adjacent bar graph. For every differentially expressed gene–PAX/CUX/ONECUT motif pair, the significance of the most significant feature linkage is indicated by a colored square.

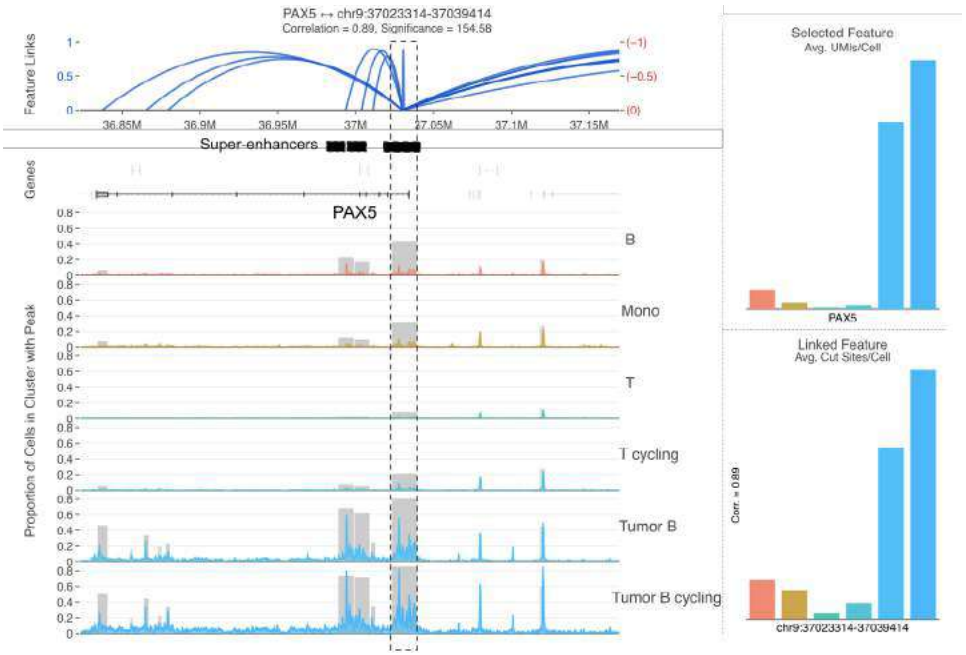


Figure 5. Loupe Browser enables visualization of feature linkages. Positively correlated feature linkages are denoted by arcs at top. Highlighted by the dotted box is a highly significant feature linkage between *PAX5* and a previously annotated CLL super-enhancer that is depicted in black (Ott et al., 2018). Below the illustrated feature linkages are open chromatin peaks identified for each cell cluster across a 0.3 Mb region. Annotated cell types are color coded. On the right are plots showing the expression level of *PAX5* (top) and accessibility of the linked super-enhancer (bottom) for each annotated cell type. Tumor B cells (blue), in contrast to normal B cells (red), have elevated *PAX5* expression and open chromatin at this super-enhancer.

Explore what you can do

Chromium Single Cell Multiome ATAC + Gene Expression helps you identify the critical regulators and pathways behind cell state. Putative gene regulatory networks can be built based on correlated gene expression and open chromatin sites with greater accuracy and confidence than would be possible with a single modality. At the same time, the identity of likely transcriptional regulators can be constrained by both expression level and motif availability. Multiomic readout at the transcriptional and epigenetic levels, particularly from the same single cell, takes much of the guesswork out of network reconstruction based on gene expression alone, enabling a deeper understanding of the molecular mechanisms underpinning disease progression, developmental differentiation, and therapeutic response.

Resources

To explore the dataset further, download the data here: https://support.10xgenomics.com/single-cell-multiome-atac-gex/datasets/1.0.0/lymph_node_lymphoma_14k

References

Ott CJ, et al. Enhancer Architecture and Essential Core Regulatory Circuitry of Chronic Lymphocytic Leukemia. *Cancer Cell*. 34: 982–995, 2018.

Contact us
10xgenomics.com | info@10xgenomics.com

© 2021 10x Genomics, Inc. FOR RESEARCH USE ONLY. NOT FOR USE IN DIAGNOSTIC PROCEDURES.

BioTechniques Spotlight

10x GENOMICS

Key trends in Multiomics

47%

47% of respondents currently use Multiomics...

31%

...31% are planning to do so in the next 3 months.

- Transcriptomics 71%
- Genomics 64%
- Proteomics 64%
- Metabolomics 42%
- Epigenomics 31%
- Lipidomics 4%
- Microbiomics 2%
- Glycomics 1%

Of those working with, or planning to work with Multiomics, 70% utilized Transcriptomic approaches closely followed by Genomics and Proteomics.

Study design

Transcriptomics was also most often selected as the central approach for multiomic studies.

- Transcriptomics 29%
- Proteomics 22%
- Genomics 22%
- Equally weighted 11%
- Epigenomics 7%
- Glycomics 2%
- Metabolomics 2%

The most common combination of omic targets studied was Transcriptome, Proteome & Genome.

Measurement types

The readouts primarily selected as the most often measured for each of the omic approaches were:

- Genomics: Single nucleotide polymorphisms 48%
- Epigenomics: miRNA 42%
- Transcriptomics: Whole transcriptome 47%
- Proteomics: Abundance 58%
- Metabolomics: Metabolite Abundance 73%

Approaches & techniques

Multiomic approaches used by respondents included:

- Multiomics from bulk data sets 34%
- Single-cell multiomics from different cells 21.5%
- Single-cell multiomics from the same cells 21.5%
- Multiomics from different cells and bulk data sets 14%
- None of the above 9%

Top single-cell and spatial technologies used in multiomic studies

- Single-cell gene expression 19%
- Spatially resolved protein detection (IF, IHC) 14%
- Other 10.5%
- Single-cell protein detection (e.g., Flow cytometry, CyTOF) 10%
- Single-cell DNA-seq 10%
- Single-cell DNA methylation 9%
- Spatially resolved gene expression 9%
- Single-cell T-cell or B-cell receptor sequencing 6.5%
- Single-cell ATAC-seq 6.5%
- Single-cell metabolomics 5%

Research fields & challenges

- Immunology 17%
- Cancer research 23%
- Stem cell biology/ regenerative medicine 10%
- Developmental biology 10%
- Other 14%
- Diagnostics/ biomarker discovery 16%
- Neuroscience 10%

The research area most frequently examined by multiomics was cancer, closely followed by immunology and diagnostics

Our respondents ranked these aspects from most to least challenging:

Most challenging → Least challenging

- Data integration and analysis
- The lack of a robust benchmark pipeline
- Study design
- Handling large data sets
- Sample preparation

The future of multiomics

What does the phrase next-generation multiomics mean to you?

Progress
High efficiency
Single-cell Multi-approach
Systems biology analysis Advancement
The complete picture
Robust
Integrative Software
Liquid biopsy techniques
Simultaneous detection
Integration High precision
Personal medical care
Promising Integrated
Complex analysis
Advance
High-throughput techniques
Single-cell New topics
Large datasets
Interesting
Progress Integrated
Analytical
Advance Whole scale
Promising
Full interrogation
techniques

The most exciting applications of multiomics

- "The opportunities for cross discipline collaboration"
- "Epigenetic applications"
- "Rare disease research"
- "Precision medicine"
- "The spatial recognition of different cell types"
- "Integrating results with data from other studies and techniques to accelerate the understanding of their biological relevance"
- "Biomarker discovery"

How do you think next-generation multiomics will advance your research?

- Increased resolution of cell populations 20%
- Gain new biological insights because you have direct linkage of different data 49%
- Increased confidence in biological insights 31%

About the respondents

Location

- 26% Europe
- 15% Asia
- 3% Africa
- 56% North America

Job title

- Department Head 11%
- Postdoctoral Fellow 7%
- Lab Director | Chief Scientist 9%
- Graduate Student 2%
- Consultant 4%
- Staff Scientist 13%
- Principal Investigator 9%
- Lecturer | Assistant | Associate Professor 4%
- Technician | Research Assistant 7%
- Professor | Instructor 13%
- PhD 4%
- President | CEO | VP | Owner 4%
- Medical Profession | Physician 2%
- Business Development Director 1%
- Lab Director | Chief Scientist 4%

Research interests

- Analytical chemistry 3%
- Biochemistry 6%
- Bioengineering and biophysics 3%
- Bioinformatics and computational biology 5%
- Cancer research 7%
- Cell biology 10%
- Chemical biology 2%
- Climate science 1%
- Clinical research 2%
- Development biology 1%
- Drug discovery and development 3%
- Genomics and genetics 10%
- Immunology 7%
- Microbiology 10%
- Molecular biology 16%
- Molecular diagnostics and pathology 4%
- Neuroscience 3%
- Plant science 1%
- Preclinical 2%
- Proteomics 3%
- Veterinary 1%

BioTechniques Spotlight

10x GENOMICS

Panel discussion

Next-generation multiomics, producing and integrating simultaneous multiomic data

In this panel discussion, we explored the techniques involved in these studies, the challenges that are arising from them and the most exciting applications of next-generation multiomics. With the insight of 4 expert panelists, the best practices for wielding multiomic approaches and integrating and interpreting the vast amounts of data produced are revealed.

Check out the panelists below, alongside some of their key quotes from the discussion. Use the QR code to watch the discussion on demand.

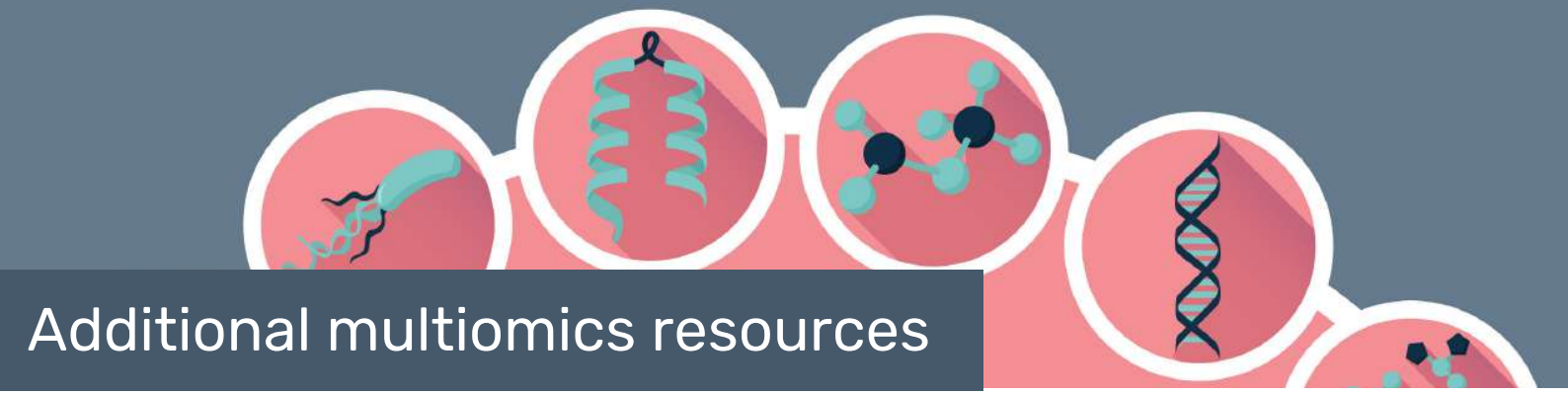
Judith Zaugg
Group Leader, EMBL (Heidelberg, Germany)
"The joy of multiomics is that it allows you to learn about a system's present, by looking at the proteome and transcriptome of a cell; the past, by examining what has been inscribed in the cells epigenome; and the future, observing how it has been primed on a genetic and epigenetic level."

Mike Stubbington
Director, Computational Biology, 10x Genomics (CA, USA)
"As a postdoc, I dreamed of a time when I could conduct high-throughput mapping of receptor sequences and their specificities. Now it's possible!"

Keri Martinowich
Lead Investigator, Johns Hopkins University School of Medicine (MD, USA)
"The combination of proteomics with spatial transcriptomics is allowing us to explore how neuropathology hallmarks like protein inclusions affect local tissue structure and cell types, and contribute to the disease process. This is really exciting to us and we think it will be huge in the neuroscience field."

Evangelia Petsalaki
Group Leader, EMBL-EBI (Cambridge, UK)
"It is a highly stimulating challenge to put all these pieces of the puzzle together to generate a picture of the whole cell, and multiomics allows us to see beyond what we could previously with only one layer of information. What's more, it opens the door to multidisciplinary collaborations and encourages scientific collaborations."

Follow the QR code to access the panel discussion:



Additional multiomics resources

You can find more multiomic resources, including White Papers, Application Notes and further eBooks and infographics, in our latest Spotlight on next-generation multiomics, in association with 10x Genomics. Check out these key highlights below.

Webinar: MultiMAP: a novel approach for integrating and visualizing multiomic single-cell and spatial data

This talk introduces a new approach for the integration of single-cell multiomics. Compared to other methods, MultiMAP is extremely fast and leverages the entire data set, enabling researchers to take full advantage of multiomic data. With scRNA-seq and scATAC-seq data generated simultaneously from the same single cells, we use MultiMAP to study transcription-factor (TF) expression and TF binding site accessibility during T-cell differentiation.

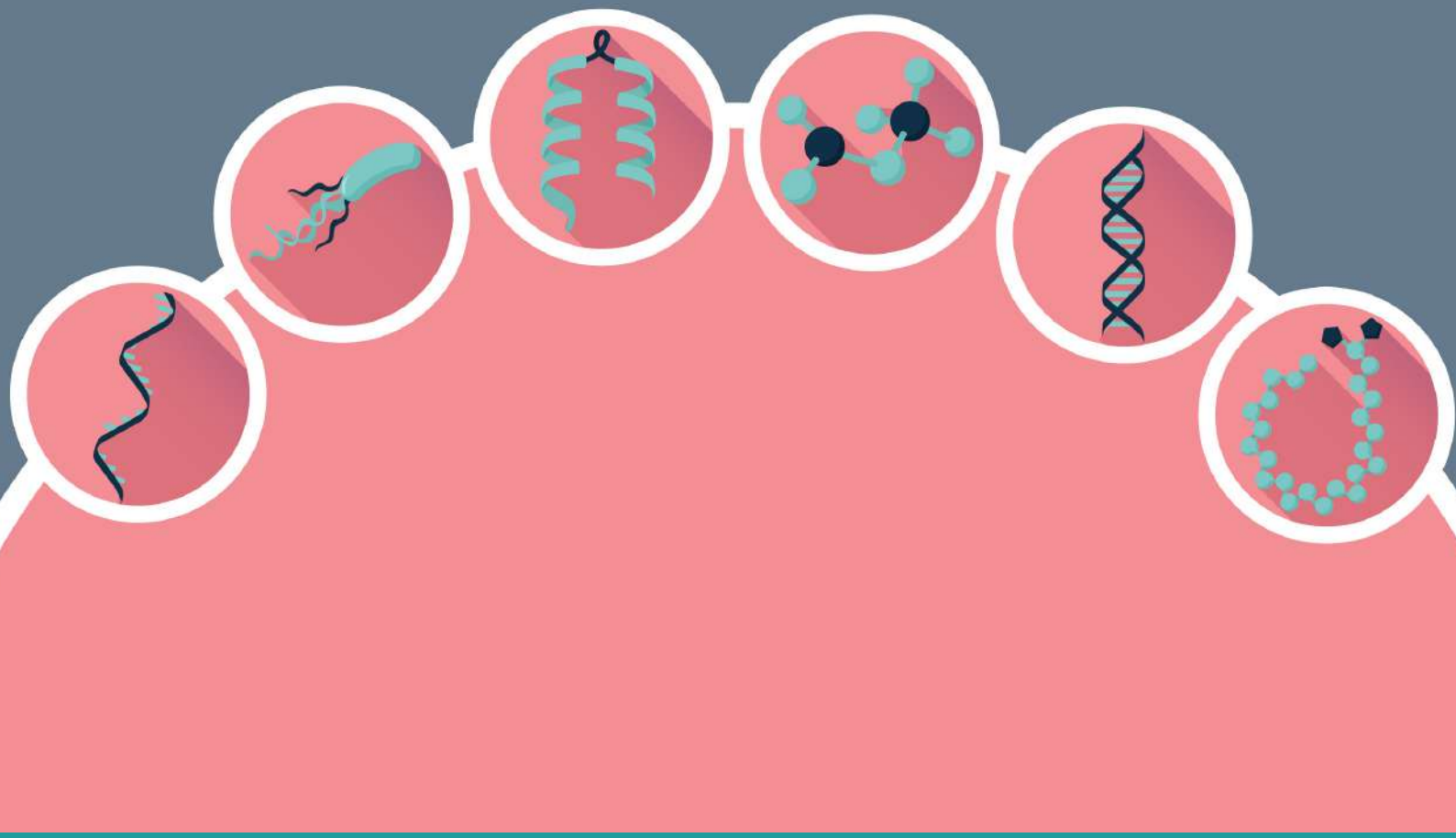
Podcast: Talking Techniques | Revealing the regulome: using multiomic approaches to explore epigenetics and DNA expression

Explore the realm of epigenetics and gene expression, discovering the different omic 'lenses' used to examine these processes and the power of single-cell studies to provide a comprehensive multiomic view of cells and their biology.

Guide: Multiomic single-cell immunology

Learn how multiomic tools are transforming the way we investigate infectious disease and immunological response in this guide. Find a detailed breakdown of single-cell solutions, sample-prep recommendations, tips for sequencing and data analysis, and an in-depth compendium of publications and resources.

BioTechniques
The International Journal of Life Science Methods



Contact us

Editorial Department

Senior Editor
Abigail Sawyer
asawyer@biotechniques.com

Business Development and Support

Commercial Director
Sarah Mayes
s.mayes@future-science-group.com

This supplement is brought to you by *BioTechniques* in association with:

10x GENOMICS