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CUSTOMER INTERVIEW

Unlocking Multiomic Insights with Bernard Thienpont

Introduction

Bernard Thienpont
Professor, KU Leuven

Professor Bernard Thienpont was trained as a bioengineer at KU Leuven. During his doctoral research, he made significant contributions to genetics, including the discovery of a new genetic syndrome and a gene that causes heart defects. He subsequently conducted research in Cambridge on the epigenetic causes of heart disease and at the VIB Vesalius Research Center on cancer epigenetics. Since 2018, he has led the Laboratory for Functional Epigenetics in the Department of Human Genetics. Here, together with his team, he aims to uncover epigenetic causes and biomarkers of diseases using advanced genomic technologies. He has authored over 100 publications and has been a (co-) investigator in more than 20 national and European projects. Additionally, he is a co-founder of the Leuven Institute for Single Cell Omics and an active member of the Leuven Cancer Institute.

Interview

Could you briefly introduce yourself and your research?

My name is Bernard Thienpont. I head the Laboratory for Functional Epigenetics and was originally trained as a bioengineer before moving into human genetics. I'm affiliated with the Department of Human Genetics, the Leuven Institute for Single Cell Omics, and the Leuven Cancer Institute.

My research focuses on two main areas. The first is cell-free DNA analysis, which is primarily geared toward biomarker discovery. The second centers on single-cell analysis, including single-cell DNA methylation and, more recently, extensive work on single-cell CRISPR screens.

Multiomics is widely discussed today. In your research, is it optional or essential?

For most of our work, multiomics is essential. It's critical to approach biological questions from multiple perspectives. DNA, RNA, or proteins alone rarely provide complete answers. Only by integrating these different omics layers can we gain a true understanding of these different omics layers are influencing each other. Both from a basic biology perspective, but also I think in terms of biomarker discovery and biomarker interpretation.

How does multiomic integration change experimental design compared to traditional single-layer approaches?

There's, I think, a few important things that have changed the way we work. Once you commit to multiomics, it fundamentally changes how you design experiments. Multiomics doesn't start at the end of the experiment, it has to be considered from the very beginning.

For example, the way you collect samples needs to bear in mind that you need to analyze both DNA, RNA and protein, so you need to be able to get as

faithful a representation of those omics layers as possible in your end sample. Then when it comes to the actual experiment, you need to bear in mind that the different omics layers, in an ideal world, are profiled in the same sample, so not on separate samples. Like this, everything is internally controlled, but this of course requires dedicated methods that allow you to profile both DNA and RNA, for example in the same sample in the same analysis.

Finally, data analysis also changes. Rather than analyzing each omics layer in isolation, the goal is true integration across layers to generate deeper biological insight.

Could you tell us about your collaboration with Illumina?

We've collaborated with Illumina over the past one and a half to two years on several products they've brought to market. One collaboration focused on single-cell CRISPR screening which relied on existing expertise within within our lab, where Illumina approached us to beta test the technology based on our existing expertise. More recently, we were also invited to evaluate their 5-base technology, which aligns closely with our in-house expertise in DNA methylation analysis.

Can you share your experience with Illumina's single-cell CRISPR and 5-base technologies?

What I really appreciate about Illumina's products is that they largely work out of the box. This was especially true for the five base technology where you can go from the start to the end of the protocol without having to think too much about it and then, in the end, you end up with the result that you were hoping for.

The single-cell CRISPR screen was a beta-testing experience, so there was more interaction with the technical development team. Even so, we achieved results that enabled meaningful biological insights into the samples we were studying.

What scientific questions were you hoping to unlock with these technologies?

Each technology addresses different scientific questions.

With the single cell CRISPR screen, I think it's a super powerful technology that allows you to go beyond the purely correlative analysis that are typically done with single cell analysis. Instead of simply creating atlases of cell types or tissues, it allows you to perturb specific genes and directly observe how those perturbations affect biological responses. This has major implications for both fundamental biology and drug discovery.

The 5-base technology, the main advantage of this technology is that it largely preserves the cytosines in the DNA. Rather than converting unmethylated cytosines, it converts methylated cytosines, resulting in a more balanced base composition. This significantly improves mutation and SNP calling compared to conventional methylation methods.

What surprised you most about the biological insights unlocked by 5-base technology?

Beyond improved mutation and SNP calling, what stood out was the ability to work with very low amounts of DNA. The protocol relies on a single DNA purification step, which minimizes material loss. Compared to methods requiring multiple purification steps, this results in a much more faithful representation of the original sample in the final sequencing library.

How critical is high-throughput sequencing capacity like NovaSeq™ X in enabling ambitious multiomics research programs?

High-throughput sequencing capacity is no longer optional for our lab- it's essential. High-throughput experiments allow us to control technical variables more effectively by relying on fewer sequencing runs. At the same time, increasing sequencing capacity has driven down costs.

Experiments that were unthinkable just a few years ago such as profiling genome-wide DNA methylation across thousands of single cells are now feasible. This shift has fundamentally enabled the research we're doing today, and this is really enabled by increase in throughput by Illumina.

Do you see multiomics becoming a routine part of translational research? What needs to happen to get there?

At present, multiomics is not yet part of routine clinical testing, but there is a strong push in that direction. One

major challenge is controlling pre-analytical factors. Most existing tests are optimized to preserve either DNA or RNA, but when we combine multiple modalities in a single test, we need to preserve all these analytes in an optimal way to get a reliable output.

In addition, we need to develop and validate multiomic biomarkers and demonstrate that they offer clear advantages over single-omic biomarkers currently.

If we revisit this conversation in three years, what do you think will have changed most because of multiomics?

Well, I think where multiomics really shines is in its ability to connect the different omics layers. By analyzing the same sample across multiple omics layers, we're able to dissect cause and effect in a much more fine grained way. This applies both to patient samples and to in vitro cultured cell lines, for example through approaches like single cell CRISPR screens. That is where I see and hope to see- the most significant advances: in the biological insights that come from approaching scientific questions through a truly multiomic lens, rather than treating them as a collection of separate single omic analyses.

Finally, what advice would you give to research groups transitioning to integrated multi-omic approaches?

My first advice is to think holistically about the whole picture. Applying a multiomic protocol alone doesn't guarantee reliable answers. Second, don't treat multiomic data as separate datasets- DNA, RNA, and protein. These layers come from the same sample, collected at the same time point, which allows you to control technical variation much more effectively. Leverage that strength and focus on integrated analysis to understand how these layers influence one another.

Learn more

Illumina NovaSeq X Series Innovation Roadmap

Illumina Single Cell Technology

Illumina 5-base Technology