Dylan Mooijman, head of R&D at Single Cell Discoveries. Video still by Illumina

The first NovaSeq X in the Benelux region is a "game changer"

Single Cell Discoveries and VectorY Therapeutics are using the power of the high-throughput sequencer to research therapies for ALS

MAURO MURARO REMEMBERS being skeptical of single-cell sequencing when he first learned about it. “You start with 0.1 picograms of mRNA, which is a homeopathic quantity,” he says. “It’s hard to imagine you can actually measure everything that’s in a cell at that level.” But then he saw how rich and multilayered a single-cell data set could be. “The biology was basically shining through the numbers on the screen. That was the pivotal moment. I was blown away.”

Watch the video at youtube.com/watch?v=z9lfJ2ENbbo

While studying for his PhD in the department of Developmental Biology and Stem Cell Research at Hubrecht Institute in the Netherlands, Muraro met Judith Vivié, manager of its Single Cell Sequencing facility. Over two years working together, Muraro and Vivié saw the demand for their services grow continuously—to the point that they could no longer keep up. And they saw an expertise gap: The lab’s clients were experts in their biological field, but they needed help from experts in sequencing technology.

Muraro had always assumed he would stay in academia. He never considered himself “the entrepreneur type.” But the opportunity was clear, so in 2018, the duo cofounded Single Cell Discoveries.[1]

“Let’s try it first and see what happens.”
Muraro and Vivié, now CEO and COO respectively, say their partnership works because of their complementary points of view. “I work in the now, and he looks more ahead,” she says. “He sees what we really need in the next step, but I’m always concerned. ‘Okay, but can we afford it?’”

1. scdiscoveries.com

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He says he errs on the side of optimism: "Let's try it first and see what happens—and that's not always the best attitude. If we had both been more conservative or more forward looking, it wouldn't have worked out."

For the first six months, it was just the two of them. She handled the lab and the operational side, and he the R&D and client outreach. As demand grew, their staff expanded to meet it.

They were able to incubate their operations in the Hubrecht Institute. At the time, they were doing their own library preparation, but even after moving into their own facility, they had to outsource the actual sequencing, which took a long time and complicated their project management. Vivié says, "What was really missing in our company was the ability to sequence. In the end, you don't want to rely on machines from a different company."

Single Cell Discoveries officially brought the sequencing step in-house when they bought an Illumina NextSeq 2000 System. And in late 2022, just as they were planning to scale up even further, Illumina debuted its highest-throughput system yet. At that point, Vivié says, "We had to go big or go home."

"That's when I realized this machine is a game changer."

Single Cell Discoveries was the first company in the Benelux region to install a NovaSeq X, and its leaders all mention how exciting that day was. Head of R&D Dylan Mooijman remembers thinking, "'We're living in the future.' We were all captivated."

When Vivié and Muraro first started working in single-cell sequencing about 10 years ago, it was a niche academic field, and only a handful of labs were interested in whether it could even be done. They could sequence maybe 100 cells in a day—"and that would be a very long day," she says. "So when Mauro had the idea to purchase the NovaSeq X, I thought it was a bit crazy, simply because we would never have that much to sequence—we would never fill 25 billion runs, let alone two of them."

But, true to character, her cofounder was thinking ahead. "It took us, I think, seven years to process 1 or 2 million cells together as a global community," he says. "Now we can do it in a weekend. It's just amazing to see how much data it produces."

That high throughput is valuable not only for its volume, but for its versatility. "Because the flow cell has eight individual lanes, we still have the flexibility to run a lot of different projects in one large sequencing run at an affordable price," Vivié says.

When Mooijman started sequencing huge projects of a million cells each—with the demultiplexing step done on the machine, with all data quality clocking in above Q30, in just two days—"That's when I realized this machine is a game changer."

All these improvements translate to happier clients. "It's much nicer to finish something days, weeks before clients would normally expect to get it," he adds. "And there are particular biological questions that can only be answered if you have that type of throughput"—questions like those being asked by one of their neighbors, just up the road in Amsterdam.

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"There's no other way to do this than by using this technology."

Sander van Deventer has worn many hats in his storied career: doctor and professor of gastroenterology, venture capitalist, and cofounder of multiple biotech companies over 25 years—most recently VectorY Therapeutics[2] in August 2020, where he's now president of R&D.

VectorY develops drugs for neurodegenerative diseases by using gene therapy to deploy tailor-made antibodies to work within single cells. Their sights are set high, on some of the most challenging conditions known to science: amyotrophic lateral sclerosis (ALS) and Huntington disease.

2. vectorytx.com

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Humans have about 90 billion neurons, only 150,000 of which are motor neurons, and only a very tiny fraction of those are of concern for ALS. The targets VectorY has identified for potential ALS therapies are aggregated proteins that are exceedingly hard to address because they're essential for neuronal function. Antibodies have proven a useful tool for working with them, because they can precisely recognize misfolded proteins from correctly folded ones.

These proteins are responsible for splicing at least 40% of mRNA transcripts in neurons. "So the readout here is not a single cell or a single protein that's nonfunctional—it's about 40% of the complete transcriptome," van Deventer says. "We want to find out whether we can repair most of that. The only way to do that is by looking at the complete transcript, and if you want to do that in a dose-dependent manner, there's no other way you can do it than by using [single-cell sequencing] technology."

VectorY tests their therapies in ex vivo systems, like induced pluripotent stem cells or organoids—which are increasingly more important than animal models. Van Deventer says they can access the entire transcriptome and proteome to precisely measure the changes caused by their drug candidates just by looking at a single cell, "where in the old days you would have to do a dose response in hundreds of mice, for example."

"We cannot afford to not produce quality data," he continues. "Because we want to be absolutely sure we've done the utmost to provide the best drug, in terms of efficacy and of safety."

So to get the highest quality data as fast as possible, VectorY works with Single Cell Discoveries.

"Science is a team effort."

VectorY Discovery Scientist Alessandro Moro has Single Cell Discoveries on speed-dial. Whenever he has an idea for a new experiment to run, he calls up Mooijman to see if they can accommodate it and, if so, what samples they need.

"I'm extremely curious to know how those neurons work and behave, so the amount of data they can provide us with simple experiments is just fantastic," Moro says, adding that sequencing with Single Cell Discoveries "opens up the door to totally new therapeutics…and even new biology."

Likewise, Mooijman agrees that VectorY is an ideal partner to work with, because they always have new and different interesting projects: "You never quite know what a client wants to do, then on the spot you have to come up with a solution. That sudden creativity of the job is what I really enjoy."

The two companies work together to review and interpret the sequencing data from their experiments—to determine the degree of dose response, sort out which cellular pathways were affected, and retool the drug candidate for the next round of experiments.

Moro is quick to note that, as crucial as the speed and accuracy of the NovaSeq X have been to the companies' projects, the lasting good they're working toward depends on more than technology: "We can be the driving force toward better therapy. We don't only have the machines to run it—we also have the mind and the personality, because science is a team effort."

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"Multiomics is not the future. Multiomics is the present."

When asked how far he thinks genomic sequencing technology will go, Muraro identifies the growing importance of analysis algorithms that are driven by AI, since they're now at the level where they can produce so much data, they need more than just human beings to make sense of it.

He also points out that some questions are best answered by integrating multiple layers of data, like epigenomics and genomics, from fewer cells: "Multiomics will be very important, to cross-validate findings from

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one data set to another and make sense of the data much quicker."

The leaders of both companies all agree with the statement that multiomics is the future—but Moro takes it a step further. "Multiomics is not the future. Multiomics is the present," he says. They already have the technologies to learn everything a single cell has to tell them—"we just need to start deploying them as soon and as well as possible, because it's not 'We have one target and that's it'—the cells are a lot more complex, and we need to start thinking as such." ◆

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