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Photo by Kristy Walker*

How two systems integration scientists ensure a smooth workflow on MiSeq i100

Dorothea Agius and Joe Cottrell talk about developing illumina's most innovative and accessible low-throughput platform

illumina recently launched the MiSeq i100 and MiSeq i100 Plus Systems,¹ two powerful, compact benchtop sequencers that incorporate more than 140 invention disclosures and 60 patent families. On our News Center, we are celebrating outstanding employees who helped develop this breakthrough technology.

DOROTHEA AGIUS HAILS from Germany, where she completed her PhD in bioinformatics at the Max Planck Institute for Informatics. Immediately after, she traveled to the US for her postdoc at the University of California, San Diego. She recalls attending a campus talk on next-generation sequencing by an illumina distinguished scientist: "I said, 'This is so cool. One day I want to do that.'"

Not long after in 2014, she got her chance. illumina's bioinformatics department hired her to computationally dissect data and address any data quality issues on its newest sequencers. Though she left the company briefly in 2021 to pursue another opportunity, she returned the next year and immediately began working on the new MiSeq i100 Series, which was just unveiled last month.

In her latest role at illumina, she has joined the Systems Integration team. The focus is still on data quality but on a much broader scale, looking at entire end-to-end workflows, and specifically as it applies to the new MiSeq i100—an easy-to-use platform with streamlined workflows and expanded output.

Dozens of experts worked together to develop the new product, including Agius's illumina colleague Joe Cottrell. Cottrell is a native San Diegan who grew up nearby, in Vista. He graduated from UC San Diego with a degree in biochemistry and went to The Scripps Research Institute (TSRI, now named Scripps Research) to study the kinetic mechanisms of RNA enzymes, also known as ribozymes.

After seven years at TSRI, he was ready for a change. One of the postdocs in Cottrell's lab, who was also his mentor, had moved to illumina. So when he got the call, he followed suit and has been with the company for 13 years, working predominantly on sequencing platform development, including all three of illumina's *in vitro* diagnostic systems: MiSeqDx, NextSeq 550Dx, and NovaSeq 6000Dx.

1. [illumina.com/systems/sequencing-platforms/miseq-i100.html](https://www.illumina.com/systems/sequencing-platforms/miseq-i100.html)

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During platform development, the Systems Integration team ensures that all an instrument's system-level components work well together. These components include end-to-end workflows, which Agius and Cottrell oversee. This requires significant focus on the applications supported by the system as well as its data quality and performance. Early in the project, this entails closely collaborating with Illumina's marketing team to identify customers' most widely used applications. "If the majority of customers say oncology is their highest priority, oncology applications must be thoroughly assessed and supported as soon as possible," Agius explains. "If many customers are interested in infectious disease, that becomes an additional main focus."

Combining the best elements

Over the years, Illumina has produced three low-throughput benchtop sequencers: the original MiSeq, the iSeq 100, and the MiniSeq. The new MiSeq i100 brings together the best elements of all three systems—the long-read capabilities of MiSeq, the two-channel chemistry from the MiniSeq, and the CMOS image capturing from iSeq—along with other improvements from more recent platforms to produce a new system.

The original MiSeq used four-dye chemistry, non-patterned flow cells, and bridge amplification. Over the years, Illumina has made strides in clustering chemistry, imaging chemistry, and our image capture process utilizing CMOS technology. "The MiSeq i100 brings all those things together in a very elegant way, which allows us to improve what the customer cares about—sequencing time, quality, and overall robustness," Cottrell says.

The new MiSeq i100 comes equipped with DRAGEN onboard. "We already know the DRAGEN solutions perform great and run very fast," Agius says. The team has loaded as much onboard as possible so the customer won't need a bioinformatics specialist. "We want our customers to be able to push a button and have the analysis issue the results without requiring in-depth computational knowledge. And the results are most likely going to look better than most software."

Index-first sequencing

The MiSeq i100 is the first Illumina platform to offer index-first sequencing. Typically, a customer will sequence a pool of libraries, not just one sample at a time. Illumina

supports sequencing up to 384 samples in a single run. To differentiate those samples for downstream analysis, they must be indexed. Technicians add adapters during library prep and make clusters, then the instruments sequence the first genomic read, followed by the index read, and then the second genomic read.

But MiSeq i100 uses proprietary primers to enable index-first sequencing, which has proven to be as robust as traditional read-first sequencing. The MiSeq i100 can give key information around sample demultiplexing performance (how well the samples differentiate between the reads) very early on in the run. If it's not sufficient for the downstream analysis, a researcher can reassess their sequencing plan.

"They'll be getting that critical information much, much sooner than they would on other platforms, especially the original MiSeq," Cottrell says.

Seeing the finished product in customers' hands

Cottrell and two additional team members each got the opportunity to visit different early-access customers, all of whom have tremendous experience with Illumina systems. Cottrell stayed close to home, visiting SeqMatic in the San Francisco Bay Area; the others traveled to Canada, Germany, Switzerland, and Australia. "We wanted to make sure the team got to be there for the first customer experiences," Agius says. "It was very rewarding for them to see our customers so excited about the new sequencer." (Read the University of Zurich's story at the URL below.)²

Cottrell was pleased to hear positive feedback from around the globe. He relays what a group of 20 in Australia said—that while only a handful of them were trained in operating the original MiSeq, they were so impressed with the accessibility of the MiSeq i100 that they plan to have everyone in the lab do runs with the new system. "That was really encouraging to hear," he says. "For us as developers, we're working on early stage, so we experience early challenges; it's not until it all comes together that we realize we really moved the needle with the customers in terms of ease of use."

He believes the instrument will inspire new customers and new applications, and will dramatically improve efficiency and throughput for existing customers, especially MiSeq customers: "They're going to be able to almost double or triple their capacity with the system. The opportunity this brings for certain applications, especially around infectious disease monitoring and

2. [illumina.com/company/news-center/feature-articles/zurich-lab-imagines-new-possibilities-in-microbial-research-and-.html](https://www.illumina.com/company/news-center/feature-articles/zurich-lab-imagines-new-possibilities-in-microbial-research-and-.html)

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specific oncology and microbial applications—it's going to be exciting." He adds that the improved data quality can unlock potential applications and data interrogation that wasn't previously possible.

"Our MiSeq customers are the most adventurous of all," Agius says. "They're using the instrument for all kinds of scientific advances and they're coming up with applications and use cases that no one has thought of. What makes the new MiSeq i100 development really exciting is that the data quality has gotten so much

better than any of our low-throughput systems currently on the market. This will translate into improvements across applications and new scientific findings. We're very confident in the MiSeq i100 and its supported applications, because we've accomplished the broadest testing we've ever done. We have put ourselves in our customers' shoes and assessed every application we could think of that a customer might want to run. We have tested everything ourselves to make sure that once it gets into customers' hands, it will work really well." ♦