Genome Editors Begin Lining Up for Inscripta's Onyx Platform

Jan 07, 2020 | Andrew P. Han

NEW YORK – Customers are beginning to line up for Inscripta's Onyx Digital Genome Engineering platform, launched in October.

The first of the fully automated benchtop instruments, designed to enable genome editing at unprecedented scale, will go to Jef Boeke of New York University in the first half of this year. "It looks very promising," said Boeke, who participated in an early-access program. The system "allowed us to look at thousands of changes in parallel," he said.

The black box, approximately the size of a benchtop sequencer, with a list price of $347,000, is perhaps Inscripta's biggest step towards its goal of becoming "the Illumina of genome editing," as CEO Kevin Ness likes to say. "Our mission is to enable customers to use biology in a majority of global markets," including energy, materials, agriculture, and pharmaceuticals, said Inscripta CEO Kevin Ness. "That's a really big statement. How do you do that?"

Onyx is Inscripta's answer, a platform comprising the instrument, as well as reagents, software, and assay kits for gene editing library analysis, that promises to be both simple and complex.

The simple part is starting with a single genome, selecting the edits to make with software, and pushing a button to get out a mix of millions of cells with up to 10,000 different genotypes. The complex part is what happens inside the box, and, according to Chief Commercial Officer Jason Gammack, wrapping one's head around what Onyx makes possible.

"When we were telling people about our science prior to the launch of the instrument, most people assumed we were offering a service," Gammack said. "And they assumed we were offering a service because they understand the absolute complexity and heavy lift of this tech. Even as people look at it, they struggle to understand how a [benchtop] box can drive the science."

For starters, Inscripta promises Onyx will be able to edit cells — yeast and Escherichia coli for now, although there are plans for mammalian cells eventually — not just with single knockouts, but multiple edit types.

"Just knocking out a gene function is not going to produce the cell features needed for all global markets," Ness said. "You have to start to introduce knock-ins, insertions, deletions, up and down gene regulation, and [gene] swaps. And a lot of times it's not going to be just one change, it's going to be a combo of multiple edits per cell. It's not just knockouts and you need that to move biology to wherever we want it to go: turning on the bioeconomy."

But even as Inscripta has plans to touch everything, the firm isn't guaranteeing that everyone who wants one will get one, certainly not right away.

"We do have a customer screening process," which was implemented with biosecurity in mind, Gammack said. "Our platform has tremendous power and that requires us to ensure it's being used responsibly. That said, our view is this is a democratization point. We just want to ensure users have experience in the art and the science and if they don't, we'll work with them to train them."

In the second half of last year, the firm was on the trail showing off Onyx at conferences like SynBioBeta in San Francisco (where Inscripta launched Onyx and was the headlining sponsor), October's American Society of Human Genetics meeting in Houston, and even November's GP Write and Sc2.0 meeting in New York.

Inscripta, formerly known as Muse Bio, emerged from stealth in February 2017, but has been working on Onyx for about four years. In December 2017, the firm released its MAD7 genome editing enzyme to the research community for free, with no upfront licensing fees or reach-through royalties on products made with the technology.

As reported by GenomeWeb in June, the platform relies on integrated barcodes that allow the system to track edits and cells in the library. Earlier this year, the firm released data on an internal large-scale experiment on engineering the lysine production pathway. In presentations at SynBioBeta, Inscripta researchers showed how in just a few months they were able to recapitulate the improvements the field had discovered over decades to generate a 14,000-fold improvement in protein yield over the wild-type strain.

In December, the firm raised $126 million in a Series D financing round, which it plans to use to commercialize Onyx and continue developing the platform.

Onyx is a move beyond the 96-well plate, using unique barcoding technologies like those akin to combinatorial indexing in next-generation sequencing and single-cell genomics. But the platform doesn't just stop there. Ness said Inscripta doesn't want to simply stick researchers with a hugely complex library of cells. "They'll need to measure the output of these large libraries, so we made a significant investment in developing additional assays" to help with analysis, he said. "They're whole new in vitro biochemical solutions and informatics pipelines that play together, reading the barcodes that are put on the editing plasmids we transform into the cells."

Inscripta has anticipated the need to genotype the "winning" edits that users screen for. These screens could be done with several existing tools, including mass spec or microscopy. For genome interrogation, Inscripta offers a hybrid capture-based assay as well as a whole-genome shotgun sequencing approach, both of which are designed for Illumina sequencing. Ness said the assays could theoretically be designed to work with other platforms, if Inscripta chose to go that direction.

But Ness stressed that no one round of edits would be enough to engineer meaningful changes in all the possible pathways and genomes. "You have to do one round, take all the lessons learned, and put them into the next round as you move up the fitness landscape," he said.

Here, scale helps change the game. "When you could only make 100 cells, you wanted to screen them all, because you're trying to find a winner," Ness said. "When we make 10,000 cells, we don't just have one winner, we have hundreds of winners. So you can [take a shallow sample] and grab a few winners, and recombine those winners in the next round."

"That's a challenge, to genotype those winners," Ness said. "This is where our assays come in. We designed the barcodes to allow you to go in with a minimum amount of sequencing and see all the genotypes that are present."

Inscripta also developed a quality control assay to make sure the editing ran successfully. The assays do not actually run on the Onyx instrument, Gammack noted.

Software is an important part of the platform, too, Ness said, and Onyx will come with three tools, the Inscripta engineering portal for designing experiments, the Inscripta Resolver for analyzing the sequencing results, and Inscripta Learn for iterative design. Gammack said that for now, the "Learn" part of the software would be enabled in future releases, but wouldn't say when.

So far, Onyx seems to have impressed, although some observers have wondered aloud how much traction the firm would get right away.

"I am impressed by the machine and the price tag is not so 'exaggerated,'" said Jae-Gu Pan, CTO at Genofocus, a South Korea-based synthetic biology company. "Yes. I would be lining up for buying Onyx," he said, with the caveat that he would be reluctant to use it with an organism actually used in producing materials. Onyx requires the user to send the entire organism's genome to Inscripta, a risk most companies simply would not be willing to take with proprietary organisms, Pan said. He'd be more likely to use an "intermediate" strain with Onyx and transfer knowledge obtained to the production strain.

"Inscripta considers security, both data security and biosecurity, a top priority for the business and has made significant investments in these areas," Gammack said. "We are committed to working with our customers to ensure their security concerns are addressed."

Early-access users from both academia and industry praised Onyx in a statement accompanying the product launch, although none responded to requests for further comments. "The Inscripta tech allows genome engineers to rationally modify targets at an unprecedented scale," Chris Voight, codirector of the Synthetic Biology Center at MIT, said in a statement.

"Inscripta's platform has afforded us the opportunity to explore the genetic dependencies of antibiotic function in unprecedented detail," said James Collins, also of MIT.

"The platform allows us to rapidly and cost-effectively engineer large numbers of genetic changes into microbial cell factories," Markus Herrgard, director of data science and automation at the Novo Nordisk Foundation Center for Biosustainability at the Technical University of Denmark, said in a statement. This will significantly accelerate our progress in creating new cell factories for sustainable production of chemicals."

Another early-access user, Chris Savile, VP of Commercial Operations at Willow Biosciences, said in a statement that Inscripta's technology "enables us to generate and screen large libraries of precisely edited strains on a scale never seen before. These unparalleled capabilities will be used to accelerate our microbial R&D programs and shorten time to market."

Inscripta declined to say how many other orders it had received, but customers that do get an Onyx will be able to access "one of the most integrated life science tool platforms that has maybe ever been created," Ness said. And it's not just a new tool to do science. Ness said Onyx enables an entirely new approach to gene editing.

"It's a hypothesis generator and validator," he said. "You don't have to spend all your time on deciding what edits to make. You can just make them all and then follow the data."