

DNA Sequencing Startups Aim to Reduce Cost, Increase Meaning in the Data



By Stacy Lawrence, June 15, 2020

Genomic sequencing has long been largely ceded to one company, Illumina. That has helped Illumina steadily reach international scale, but its singular market dominance has limited investment in further advances to genomic sequencing technology.

Signs of change are now starting to appear. One of the top performing IPOs of last year was for 10x Genomics. The Pleasanton, Calif.-based company (market value: \$8.3 billion) has emerged with its single cell sample prep and analytics technology that sits on top of sequencers marketed around the world by Illumina.

That success, alongside ongoing rapid advances in computing power as well as artificial intelligence and machine learning, seem to have sparked more interest in next-generation sequencing--which is now on its fifth iteration, having started to [merge fully into multi-omics](#) with in situ RNA analysis at a single cell level.

In addition to multi-omics, the latest crop of genomic sequencing startups is working to make the technology faster, cleaner, cheaper and more meaningful. The ultimate goal is to make genomic sequencing more widely available. Eventually, proponents hope, genomic analyses will be fully integrated into routine clinical care for patients.

Existing oncology genomic panel assays such as those from Foundation Medicine are looking for specific, known mutations, and even those commonly aren't used in accordance with standard medical guidelines. But mass-scale, inexpensive analyses of whole genomes could unlock the understanding of genomics in a way that could make predictive and personalized medicine a routine reality.

First, some things need to happen with the underlying technology.

Molecular electronics

That's the ambitious goal of San Diego-based Roswell Biotechnologies, whose very name suggests a fundamental shift in the way reality is understood. The founders have worked for years to make their vision of molecular electronics a widespread, inexpensive means to sequence whole genomes. It's aiming for a one-hour, \$100 whole genome sequencing that can be conducted on small, easy-to-use equipment.

"Our first real battle we want to wage is helping create that knowledge base, so that all of these programs going on to sequence millions of genomes really can proceed forward and sequence millions of genomes; they need a much lower price point," said Dr. Barry Merriman, co-founder and CSO of Roswell.

"The other aspect that we are trying to directly address is really around simplicity. What that means is we need to make a device that has a very simple workflow, that does not require a PhD-level person to actually operate it," continued Paul Mola, co-founder, president and CEO of Roswell. "It's got to be very easy to use. It's going to take a very small footprint machine that sits in a corner in a doctor's office or in a lab--and not be high cost in terms of the total cost of ownership."



Roswell Biotechnologies co-founders. CSO Barry Merriman at left and CEO Paul Mola at right.

Most recently, Merriman and Mola worked as part of geneticist Craig Venter's anti-aging startup Human Longevity. They've been at it for years. They had initially met at Life Technologies when it acquired Ion Torrent Systems, which was the first company to put DNA sequencing on a CMOS chip, in 2010 for up to \$725 million.

After that, they worked with the Ion Torrent technology and the government of Saudi Arabia in a scheme to get whole genome data for their entire population. The price then of \$1,000 per person was still not feasible at such a large

scale. Then in 2014, they founded Roswell to continue the work; early last year it secured a \$32 million series A round.

Roswell's ENDSeq System (Electronic Nano-Device Sequencing) provides real-time monitoring of polymerase activity that is integrated into a nano-circuit for DNA sequencing. The nano-scale molecular electronic sensor to read DNA is part of a massively parallel sensor array on a standard type of semiconductor chip, known as CMOS.

"It was clear that the whole genome was still not viable--and that it would still be just a portion of the genome, not the whole genome," said Mola. "Using chip-based sequencing, we realized that was not good enough, but there was not chemistry that was fully compatible with CMOS. With the Ion Torrent chip chemistry, it was a sort of a bead. The way you shrunk it was to make the bead smaller, you just hit a limit where the bead could not shrink any smaller and chemistry did not scale."

"Around 2014, the pieces came together, where we had a chemistry that was fully compatible with CMOS technology. The idea was that if you had a chemistry that has single molecule sensitivity and that was actually a nano-chemistry in dimensions, which meant that it was fully compatible with CMOS," continued Mola. "The chemistry is molecular electronics; it's all about taking a single molecule and integrating it into a nano-packet and putting that nano-packet on a CMOS device and scaling it."

Advancements in nanotechnology, CMOS and chemistry all came together to make this possible.

By the end of next year, Roswell aims to begin marketing a system that is capable of a whole genome analysis conducted in one hour for about \$100. It could one day cost as little as \$10, the company suggests. An equivalent quality whole genome analysis via established technologies would currently cost roughly \$30,000-\$50,000, the company noted.

Notably, Roswell is not alone in saying a \$100 whole genome analysis is here. A couple of Chinese companies MGI and BGI also reportedly said they have that capability as well at this year's Advances in Genome Biology and Technology (AGBT) conference.

Linked long-read improved

Another startup, Universal Sequencing Technology (UST) of Canton, Mass., aims to make linked long-read sequences, of the sort that have helped to catapult 10x Genomics, easier to do, more scalable and less expensive. It's being built by a team from 454 Life Sciences, a genomics startup that was acquired by Roche in 2007 and later shuttered in 2013.

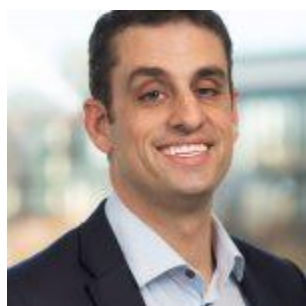
"We started relatively late. We were very excited with the long, linked-read method, but were seeing its limitations. People have to buy very expensive instruments, but the initial protocol only works for large genomes," said UST CSO Zhoutao Chen. "And with the procedure there were customer complaints and results not that are not that consistent."

“So, we developed the TELL-SEQ technology. The fundamental concept is a linked read output, we can do all directions in a single tube. We don’t need any extra expensive instruments like 10x, we just use the standard molecular lab equipment and in three hours we can get the sequencing library.”

Transposase Enzyme Linked Long-read Sequencing (TELL-Seq) is all carried out in a PCR tube and can be adjusted to the size of the analyzed genome. It can generate an Illumina sequencing library in three hours. UST hopes that TELL-Seq will become the new standard library method for whole genome sequencing.

TELL-SEQ was rolled onto the market late last year. Beyond whole genome sequencing, it aims to apply the technology also to exome sequencing and more targeted applications such as the human leukocyte antigen (HLA) region of the genome.

Double strand analysis



Jesse Salk, CEO and CSO,
TwinStrand Biosciences

Greater accuracy in substantive genomic detail is the primary goal of Seattle-based TwinStrand Biosciences. The University of Washington spinout received a \$16 million series A round early this year to get it to commercialization of its Duplex Sequencing technology. The platform works by analyzing both strands of individual DNA molecules and then comparing the results to more effectively eliminate analytical errors.

“How do you detect a small amount of one genetic variant mixed in with a lot of something else? For example, one cancer cell--that one mutation makes it a cancer cell, but it's mixed in with 100,000 normal cells,” said TwinStrand founder, CEO and CSO Jesse Salk, who developed the technology in medical school. “How can you pick that out? The standard way of doing next-generation DNA sequencing is really good for screening large swaths of the genome and looking at genetic difference between Person A and Person B identifying a gene that's associated with schizophrenia or something like that, where all the cells have the same sequence so it's technically very easy.”

“It’s much harder if you have a little bit of one thing and a lot of something else, because the error rate at the machine is somewhere in the range of 100 to maybe one in 1,000 in the very best case scenario. So if you're looking at one in 100,000, and your error rate is one in 100, your background noise from errors is far higher than signal and you can't detect it.”

The platform is designed to find ultra-low frequency DNA mutations with a resolution that’s 10,000-fold more sensitive than standard tools. That can be useful across a variety of applications including drug development, early cancer detection, residual cancer monitoring after treatment and genetic toxicology.

“This is an area in oncology where new targeted drugs are very effective, but natural selection can kill all the cells that are sensitive and cause relapse. We can see that resistance coming months in advance,” said Salk, who remains a practicing oncologist. “The advantage of that is there are often second- or third-line drugs that are not cross resistant. Companies developing second, third, fourth generation drugs need to be able to identify the people who are at highest risk of this happening to really speed up their trials and they can make it to market faster.”

He noted that some combinations of HIV drugs have been found to slow the development of resistance in certain patients--he expects that if oncology combinations could be similarly optimized based on early response that could substantially slow the development of resistance.

Nanopore chips+polymer

Roche aims to build a better nanopore sequencer. To do so, it recently acquired Seattle-based Stratos Genomics. It is now merging it with another startup, Genia, that it acquired in 2014 that has a single-molecule, semiconductor-based, DNA sequencing platform.

Stratos has worked for years on what it calls an Xpandomer. It is a highly measurable surrogate polymer that uses a simple biochemical reaction to encode the sequence of a DNA molecule. It encodes sequence information in high signal-to-noise reporters to enable highly accurate, single molecule sequencing in a low-cost nanopore instrument.

Neil Gunn, Head of Roche Sequencing explained, “Roche first got involved with Stratos in 2014. At that time, we acquired Genia as a nanopore platform, and the concept of the Xpandomers and nanopore platform was always self-evident, and it was our first link to Stratos.”

“We remained in contact throughout as their technology developed,” he continued. “Then the timing was right to acquire them a couple of weeks ago and we closed that deal so that we can now link the two technologies together. That is the ability to get the Xpandomer chemistry running on a high-density nanopore chip. So with those two in combination, then you have a very powerful solution.”

It’s not clear yet what could drive the integration of whole genome or whole exome data into patient care. Drug developers often remain reluctant to conduct these analyses and tend to limit them to subsets of larger clinical trials, if they conduct them at all. Payers, particularly the short-term minded ones in the U.S. where patients cycle in and out of a particular insurer every few years on average, are likely to prove resistant to such testing even at a low cost.

This sort of data has yet to be collected and analyzed at scale, thereby potentially making it more difficult to determine its usefulness. Roswell’s Mola expects that population-level genome studies will be a first step, but he ultimately expects that patient groups will be in a position to drive large-scale sequencing as costs fall. They, in turn, may be able to document enough relevant information to encourage more routine drug developer and physician use of whole genome and whole exome sequencing.

“We’re seeing that as medical conditions are being successfully treated, there are certain diseases that are no longer just one disease,” summed up Gunn. “Twenty years ago, breast cancer was considered to be one disease. Now, you look at and there are so many different natures and types of breast cancer--and even those are now being reclassified. We are seeing a greater level of complexity of diseases. Whether they are genetic, hereditary, whether it’s oncology, inflammatory, or cardiac diseases, we are seeing more and more have a genetic disposition that is either hereditary or induced. So, we see genetic sequencing as being central to core diagnostics moving forward.”