Sequencing drives innovation

It took 10 years and $2.7 billion to sequence the first human genome. Today, that same sequence can be read in a single week for one-millionth the cost, as little as $3000. Genome science has arrived.

What does this mean for biology? Because of astonishing advancements in sequencing technology, an entirely new field called genomics has come to life. It has enabled scientists to spell out the genomes of organisms across all branches of the tree of life, from yeast to plants to animals. The broad goal of this young field is to understand how changes in genetic information affect life. It is applied to single cells, individual organisms, even entire species. Genomics enables researchers to understand how breast tumors develop from an initial set of genetic errors. It also enables scientists to reach back through eons of time to understand how species evolve.

In labs around the world, sequencing technology has become a staple of basic and applied genomics research. At Cold Spring Harbor Laboratory, the same technology is also being used in creative and unconventional ways that reflect this institution’s unique collaborative culture. The Laboratory has had the foresight to plan and build a cutting-edge genome-sequencing “core” facility that is available to every member of the facility and, unlike most sequencing facilities elsewhere, is fully integrated into every facet of research on the campus.

Moving beyond the straightforward compilation of genomic sequences—“read-outs” of the myriad individual DNA “letters” that make up individual genomes—CSHL scientists are developing new sequencing applications that have already generated impressive scientific results. They have found a gene that substantially increases tomato yields. They have identified a DNA element that pushes leukemia cells to keep growing. They are exploiting sequencing expertise to draw a complete circuit diagram of the mouse brain. And they are developing new diagnostics to improve cancer treatments that will cost as little as $10.

“Our core facility, the genome sequencing facility at Woodbury, has changed the way we collectively think about science,” says Professor Richard McCombie, a pioneer of genomics and genome sequencing and director of the facility. “Because of our small size, we are flexible, cost-effective, and constantly at the forefront of technology. If somebody has an idea, we can jump on it—which provides a huge advantage to our researchers in this rapidly evolving scientific landscape.”

The dawn of Next-Gen sequencing

Our genetic information is stored within our DNA, a long molecule that looks like a twisting ladder, whose runs are made up of four chemicals called bases. The full human genome is composed of 3 billion bases, whose sequence, among other things, encodes some 20,000 genes. Roughly one out of every 1,000 bases varies from person to person. This means we differ from one another by about 3 million bases over the length of the genome. Inevitably, these single-base variations affect the way our genes are used (or “expressed,” in the language of biologists). These differences are also what make each of us unique.

The first genomes were sequenced with technology that now seems quaint. In the early 1990s, researchers at CSHL worked in shifts around the clock to load DNA samples onto machines. At full capacity, they might be able to read 1–2 million bases a day, amounting to just 60 million bases a month. At that rate, it would have taken 50 years to read a full human genome.

The remarkable technology that makes this feat possible is known prosaically as Next Generation Sequencing (NGS, or “Next-Gen”). On average, it takes a little less than two weeks to sequence a single human genome, and each machine can process six genomes at once.

“We have 10 ‘Next-Gen’ machines in our Woodbury core facility,” says McCombie. Each one costs about $750,000, a steep price for individual researchers to pay on a lab-by-lab basis. “We pooled our resources—both in terms of finances and brain-power—so that our researchers have tremendous access to sequencing power, better than some of the largest institutions in the world.”

“Our genomics investigators benefit from the large number of machines at their disposal, while scientists with smaller projects—even a single experiment—also have direct access to this technology, which is unusual.” This, in turn, encourages creative applications of the technology, two of which are described below.

Using sequencing to map the brain

In one example, CSHL Professor Tony Zador, a neuroscientist, is using Next-Gen sequencing to determine how all of the neurons in the brain are connected. A map of the “connectome” will provide us with a better understanding of how the healthy brain works. But also, notes Zador, “we are beginning to understand that autism, schizophrenia and many other mental disorders are actually wiring problems in the brain. Projects like this one will help us pinpoint what goes wrong, and develop treatments for these illnesses.”

The project, though simple in concept, is actually daunting in technological terms. There are more than 10 million
Meet Mike Ronemus, a research professor at CSHL. Mike is also a father—to a young boy with autism. “For me,” he says, “this is not just a job; it’s personal.”

Cold Spring Harbor Laboratory has one of the world’s largest and most successful research programs in autism genetics. Ronemus and his colleagues, led by Professor Michael Wigler, are using Next-Gen sequencing to comprehensively search for DNA mutations in autistic children. The team has discovered that autistic children have a higher rate of spontaneous DNA mutations—“new” mutations that don’t occur in either parent. This information is already changing how we think about autism spectrum disorders.

Ronemus filmed a Public Service Announcement with Cablevision to raise awareness and support for autism research at CSHL. “All this is possible because of contributions from private foundations and individuals—including my own,” he says. Check out the PSA online at cshl.edu/mike/.

Jaclyn Jansen