Crispr Offers a Leap Forward for Diagnosing Disease

Scientists are hoping it can detect deadly ailments faster, cheaper and more accurately than current tests

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Researchers at the Broad Institute of MIT and Harvard used Crispr technology to help develop a highly sensitive test that can quickly detect small amounts of Zika virus in someone's blood.

WHEN IT COMES to treating deadly diseases, scientists are always looking for a method of diagnosis that is fast, cheap and accurate. Now, they may have found it in an unlikely place: Crispr.

Crispr, which stands for Clustered Regularly Interspaced Short Palindromic Repeats, is part of the immune system of bacteria. It works by capturing an invader's DNA and integrating it into the genome of the bacteria to help fend off future attacks. For bacteria, Crispr serves as a kind of immunization card.

While scientists have studied the Crispr system for years, they only more recently started unlocking its broader potential as a technology. The breakthrough came after a group of scientists led by Jennifer Doudna of the University of California, Berkeley, and Emmanuelle Charpentier, then of the University of Vienna, published a paper in 2012 demonstrating how to reprogram one particular Crispr system, Crispr-Cas9, to enable the editing of genes. Shortly after, in 2013, several groups reported using Crispr to edit genes in mammalian cells. Crispr diagnostics, an area of interest to some researchers early on, largely got pushed aside in the frenzy that followed.

Zika test

Then, following an outbreak of the Zika virus in Brazil in 2015, a team of researchers led by James Collins of the Massachusetts Institute of Technology and Harvard University started developing a new Zika test. They wanted something that could be deployed to remote locations and offer rapid detection. When discussions turned to how to also enable distinguishing between the African and American strains, one of the researchers proposed Crispr. Last year, the Collins lab published a paper on its Crispr Zika diagnostic.

Since then, interest in advancing Crispr's usefulness in diagnostics has grown. The goal is to develop tests that can be used in the field, and eventually at home, without requiring analysis by specialized technicians or access to labs, as current blood tests do. "What Crispr allows is the democratization of measurement," says Dan Wattendorf, director of Innovative Technology Solutions at the Bill & Melinda Gates Foundation, which has provided funds for Crispr-based diagnostic development.

Crispr-Cas9, the best known of the Crispr systems, can be programmed to insert, edit, or delete a gene in an organism's genome and has caused enormous excitement among scientists. In the lab, Crispr has helped correct mutations in human cells that cause diseases like sickle cell anemia or cystic fibrosis. Crispr systems operate using different proteins or enzymes, known as Crispr-associated proteins, or Cas.

The possibility of someday curing disease or making changes in the genome of embryos has spurred huge investment—but also a contentious patent battle for control of the technology, and an ethical debate about how, and when, Crispr's gene-editing capacity should be used.

New discoveries that could lead to even more diagnostics keep coming.

Meanwhile, as new Crispr proteins have been discovered and their properties analyzed, scientists working in a number of research labs now realize that Crispr's unique aspects offer a new approach in diagnostics.

Guillaume Lambert, who runs a lab at Cornell University, says his group wants to use Crispr to detect antibiotic-resistance genes, so that patients don't lose time, and continue infecting others, while taking a drug to which their particular strain of bacteria won't respond. "This is a potentially dangerous treatment delay," says Dr. Lambert, a former member of the Collins lab who helped develop the Zika test while there.

Keith Pardee, an assistant professor at the University of Toronto and a collaborator on the Zika Crispr diagnostic, says he is principal investigator on a project being funded by the Canadian Institutes of Health Research and the International Development Research Centre to launch what is believed to be the first clinical trial of a Crispr diagnostic. The trial is expected to start in 2018.

Expanding boundaries

The trial, which will include the Collins lab, five labs in Latin America, and others, will test the diagnostic on patient samples in Ecuador, Brazil and Colombia. The scientists involved are discussing detection not only of Zika but also related viruses such as dengue, Chikungunya virus and yellow fever, Dr. Pardee says.

Discovery of Crispr proteins besides Cas9 has also helped spur research in Crispr diagnostics. In 2016, Dr. Doudna's lab published a paper demonstrating how Cas13a may be useful to detect sequences of RNA in a virus. (RNA carries genetic information from DNA and catalyzes protein synthesis in the cell.)

Unlike the better known Cas9, which makes a specific cut in a DNA sequence then stops at its target, a key feature of the Cas13a enzyme is that it keeps on cutting. The continued chewing of RNA along with the original target—the Berkeley researchers call the enzyme a kind of molecular Pac-Man—allows for the possibility of detecting a virus even when smaller amounts of RNA molecules are present.

Dr. Collins says he was working on improving his group's Zika diagnostic when a colleague, Feng Zhang of the Broad Institute of MIT and Harvard, reached out after reading his paper. Dr. Zhang, a pioneer of Crispr-Cas9 gene editing, was also working on developing a Crispr diagnostic. But he wanted to use Crispr-Cas13a, not Cas9, and suggested to Dr. Collins that they combine their efforts.

Enter Sherlock

Earlier this year, their labs announced the creation of a new diagnostic platform with the ability to identify different viruses based on extremely low amounts of RNA in blood and urine samples. It works in a regular test tube or on special paper activated using body heat. The scientists looked for a catchy name for the platform, and chose Sherlock, for Specific High-sensitivity Enzymatic Reporter unlocking.

Sherlock, Dr. Zhang says, allows detection of a virus down to a single molecule of RNA, an important factor in a disease like Zika, which can make someone very sick even when only a small amount of virus is present. The new test, adds Dr. Collins, "is 1,000 times more sensitive than what we did with Zika."

New discoveries that could lead to even more Crispr diagnostics keep coming. Last month, Dr. Doudna and her Berkeley group published a paper that describes 10 new Crispr enzymes, all variations of the Cas13a protein. The discovery, the scientists report, opens up the possibility of a diagnostic that can detect and distinguish between two different viruses in a single sample.

Gene editing is likely to remain at the center of Crispr's appeal, because so many are drawn by the idea of changing the genetic destiny of humans. But Dr. Doudna says the work on diagnostics is a chance to "circle back" to the beginning of the discovery of the technology and create low-tech, inexpensive tools to diagnose disease. "It's tantalizing to go after that," she says.

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The Ways AI Is Transforming Drug Development

Pharmaceutical companies hope computers can accelerate the discovery process and yield more effective medications

BY DANIELA HERNANDEZ

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Randell Sanders, a cancer patient, is contributing lab samples to a study of AI and drugs.

ON A RECENT Friday in Boston, Randell Sanders gave a nurse two samples of his blood, plus a sample of urine and saliva. Clinicians would test some of the samples to see how he is responding to treatment for pancreatic cancer.

But samples also were sent to a lab where computers using artificial intelligence are changing the way pharmaceutical companies develop drugs.

The idea is that machines, which are adept at pattern recognition, can sift through vast amounts of new and existing genetic, metabolic and clinical information to unravel the complex biological networks that underpin diseases. That, in turn, can help identify medications likely to work in specific patient populations, while simultaneously steering companies away from drugs that are likely to fail.

In the past, drug companies have used artificial intelligence to examine chemistry—whether a drug might bind to a particular protein, for instance. But now the trend is to use AI to probe biological systems to get clues about how a drug might affect a patient's cells or tissues.

Biological insights driven by machine learning also could help pharmaceutical companies better identify and recruit patients for clinical trials of therapies most likely to work for them, perhaps boosting the chances of those medications' getting approved by regulatory agencies such as the Food and Drug Administration.

Data from the samples produced by Mr. Sanders, 64, a U.S. Navy veteran, will become part of the database in a $17 million, seven-year study known as Project Survival, bankrolled by **Berg**, a Framingham, Mass., biotech firm that is one of several companies in the U.S. and Europe using AI to make drug research and development less expensive and more efficient. Mr. Sanders says he agreed to take part in the study in hopes that it might "help the next person." Intelligent machines will scour his samples and genes, along with those of hundreds of other patients, for molecular fingerprints, or biomarkers, that could later be used to help measure a specific drug's impact and to identify patients in which such a drug is likely to be most useful.

The big difference between AI-driven drug trials and traditional ones, says Niven Narain, chief executive of Berg, is "we're not making any hypotheses up front. We're not allowing [human] hypotheses to generate data. We're using the patient-derived data to generate hypotheses."

Broad AI effort

Project Survival is part of a larger research program to develop therapies with the help of intelligent machines. Other efforts to leverage AI technology in pharmaceutical research include using it to find new drugs or new uses for already approved medications, as well as speeding up clinical trials by improving patient recruitment and site selection, according to a May 2017 report by analyst Datamonitor Healthcare.

Some companies, such as **Numerate** Inc. in San Bruno, Calif., and **BenevolentAI** Ltd. in London, are developing their own molecules and licensing them to drug-industry clients. Others, such as **International Business Machines** Corp., **Atomwise** Inc. in San Francisco and **Insilico Medicine** Inc. in Baltimore, are forming research partnerships with universities and nonprofits or setting up AI services aimed at drug companies.

For example, **Merck** & Co. is using Atomwise's deep-learning technology to identify compounds that could be developed into medications for neurological conditions, according to David Rosen, an associate principal scientist at Merck Research Labs in Palo Alto, Calif. Recently, there's been growing interest in leveraging this type of AI for health-care applications, in part due to the vast improvements deep learning has enabled in applications like machine translation and computer vision, which also rely on pattern recognition.

In January, **GlaxoSmithKline** PLC and Lawrence Livermore National Laboratory in Livermore, Calif., announced a partnership to use AI for pharmaceutical R&D. The consortium is in the process of securing work space in San Francisco and signing on other collaborators, according to John Baldoni, GSK's senior vice president of platform technology and science. The aim is to use AI to cut development time down to a single year, from more than 10 in some cases, he says.

In Europe, scientists are getting ready to launch a similar initiative, which will include **Johnson & Johnson**'s **Janssen Pharmaceuticals** division, plus several other drug companies and academic researchers, according to several people familiar with the matter. Janssen declined to comment on the partnership.

The uptick in interest in AI is a convergence of a few forces, says Sastry Chilukuri, a partner in the pharmaceuticals and medical-products practice at the global consulting firm McKinsey & Co. These forces include the recent availability of "enormous volumes of data," advances in computing power and AI algorithms, and the pharmaceutical industry's decadelong struggle with productivity in R&D, he says.

The rise of precision, or personalized, medicine, is also putting pressure on drug developers, steering them away from a one-size-fits-all model.

"We know that the same disease is not the same in every patient," says Andrew Stern, director of novel therapeutics at the University of Pittsburgh's Drug Discovery Institute. With care becoming more individualized, markets for some drugs are likely to "be relatively small compared to what we've seen in the past with blockbusters," he says. But development costs are "probably not going to be that different" if the R&D process stays the same, he adds.

Hence the hope that AI will reduce the cost of developing new drugs. There is scant data so far to support the premise that AI will lower costs, partly because commercializing new medications takes so long and the recent move toward AI-aided biology is relatively new.

"R&D pipelines run for about a decade," says McKinsey's Mr. Chilukuri. Thus, benefits "will play out in the next 10 to 15 years," he says.

The boost in value to the pharmaceutical industry in the medium term could be the equivalent of a 5% to 10% increase in sales, Mr. Chilukuri says, though "longer-term benefits will exceed that."

Early benefits

Some drug developers say they're already seeing early benefits.

Janssen uses AI in "the vast majority of projects," says Hugo Ceulemans, scientific director of discovery data sciences. AI systems trained on various data sources, including preclinical data sets, have helped make "significant performance improvements" by enabling "better selections of which compounds to...make and test" in the lab and by "flagging" whether compounds might have "toxic" effects or "unexpected favorable" ones, he says.

At Berg, Dr. Narain says AI has helped scientists "decide which cancers we were going to go after" by helping them understand how a drug in clinical testing might work at the cellular level. Berg's system first identifies genetic and other markers among sick and well patients by drawing on detailed medical histories as well as data from scientific publications and chemical databases. It then ranks the genes, proteins or metabolites it finds according to their relevance to a particular disease, and determines when specific genes or proteins are associated with certain patient outcomes.

Such screening is "at least 50% cheaper" than traditional methods, says Dr. Narain.

Multiple hurdles must still be overcome for AI to fulfill its potential in pharmaceutical R&D. For instance, data sets, even within the same institutions, can be fragmented or stored in incompatible ways, making it difficult for machines to make sense of them unless significant efforts are made to harmonize the data, according to Olexandr Isayev, an assistant professor in machine learning at the University of North Carolina, Chapel Hill.

Data privacy is also a concern, scientists say, especially given recent cyberattacks on health systems around the world.

Then, there's the drug-approval process, which requires data from animal and human experiments, making it unlikely computers will completely replace scientists soon.

The FDA encourages companies "to improve efficiency of identifying potent and safe molecules," says Peter Stein, deputy director of the office of new drugs at the FDA's Center for Drug Evaluation and Research.

But, Mr. Stein adds, FDA standards for clinical trials and the drug-approval process "are not different based upon the particular discovery strategy."

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