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By Sten Stovall

PACBIO AND WELLCOME SANGER INSTITUTE TELL Scrip why they've teamed up to decode genomes of more than 3,000 bacteria, including some of the world's most dangerous, and how it will help fight AMR and bioterrorism.

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The genomes of 3,000 living bacteria, some hugely dangerous and more than 100 years old, have been decoded in a collaboration between **Pacific Biosciences of California Inc.** and the UK-based the Wellcome Sanger Institute in an effort able to better understand the diseases and how they become resistant to antibiotics.

The duo are doing that by accessing Britain's National Collection of Type Cultures (NCTC), the oldest established collection of bacteria in the world, contents of which include deadly strains of plague, cholera and dysentery.

The NCTC, set up in 1920, is already widely used by researchers to compare historical and modern strains to better understand the epidemiology, virulence, prevention and treatment of infectious diseases.

All so-called 'type strains' of bacteria contained in the collection - the first strains that describe the species and are used to classify them - were sequenced as part of the genome decoding initiative by the Wellcome Sanger Institue using PacBio's technology platform.

Leaders of the project told *Scrip* that the genome sequences of these highly valuable strains are fundamental for developing ways to identify specific infections in people, including tests diagnosing bacterial infections in the field to rapidly identify the source of an outbreak and help contain infections.

The effort's insights could, if needed, also offer better responses to eventual man-made agents used in bioterrorism, they said.

They likened their project in some ways to studying fossils to better understanding the present.

"It's like a fossil from an historical point of view, but unlike with fossils where you have just a few bones from which you try to understand and replicate the whole original body, this collection is composed of bacteria that's still alive, so here we basically get the whole fossil, but in living form, and so all the information," Jonas Korlach, chief scientific officer of PacBio told *Scrip* in an interview.

The NCTC collection of reference bacteria goes back 100 years and is one of the first collections of pathogenic bacteria.

"It contains bacteria isolated from before we started using antibiotics and before we started using vaccines," said Julian Parkhill, senior group leader at Wellcome Sanger Institute.

"If you want to know how bacteria have evolved to become resistant to antibiotics and how they've evolved in response to vaccines, you need to know what they looked like before you started using them."

"This sequencing of the genomes in this collection tells us how bacteria over time have dealt with our introduction of antibiotics and vaccines - and will hopefully instruct us on how to get around those resistances," Parkhill added.

The NCTC collection now contains genomes of some 5,000 bacteria, of which 3,000 have been decoded by the Wellcome Sanger Institute using technology provided by PacBio.

“We have prioritized mainly on scientific value and scientific interest, as well as historical interest,” Parkhill explained. “The samples are stored and managed by Public Health England in very secure accommodations. Preparation for the sequencing of the DNA was prepared there, the actual sequencing was done at Wellcome Sanger Institute where dozens of scientists have contributed to the effort,” he said.

Genomics has in the past been used to identify the source of pathological threats due to its value in understanding the origin of organisms. This historic context could be very valuable in assessing bio-terror agents and their sources.

“A case in point was the US anthrax attacks where genomic data was used to pinpoint the source of the bacteria. So having these reference collections would allow more accurate assessment of the source of any eventual biological threat,” Parkhill said.

He said PacBio’s technology was chosen for the project because, “if you’re trying to generate reference genomes - genomes that are going to be valuable to as many people as possible, with as much information in them as possible - then Pacific Biosciences have the edge in terms of generating more complete data.”

The NASDAQ-listed group’s sequencing genomics technology enables real-time analysis of DNA synthesis.

It can be used in human biomedical research to resolve heritability and variant types across populations or disease states, applied in plant sciences and agriculture, for crop and livestock research acceleration via sequencing and transcriptome analysis. And the technologies can also be used to characterize viruses and microbes of infectious disease, enabling the design of better vaccines and treatments.

The group’s CSO Korlach said Pacific Biosciences was very keen to partner on the project - not because they’ll get any direct commercial benefit from it, but rather because the project “demonstrates the value of PacBio’s sequencing approach” over that of competitors.

“In genome sequencing there are four criteria that you want to look at that determine the quality of the results,” he told *Scrip*. The first is the length DNA to be sequenced. Next is the accuracy of the genome sequence. Third, is whether there is a hole or gap left in the genome; and fourthly, can chemical modifications on the DNA be measured or detected, he said.

“Those are the four criteria that scientists like Julian’s team look at. If you only have two or three of the four criteria, you’re going to be missing something. Either gaps in the genome, or it’s going to be highly fragmented, or you’re not going to see the epigenome. So the reason they chose PacBio technology was because we strive for the highest quality in all four of those areas, which gives the highest quality result,” he explained.

Korlach said his company is interested in helping to generate the database of decoded dangerous bacteria genomes “because people then see the value of having the complete genomes of all these bacteria, which is now becoming the new gold standard for this process. People will hopefully then come to PacBio in future for their microbe sequencing needs and then compare them with the 3,000 database.”

Summing up the value of the project’s genome decoding, he said that “by having this collection it gives the pharma industry and hospitals a much better idea of what you’re dealing with. And in the context of anti-bio-terrorism, it gives you an immediate understanding of whether a bug has been manipulated by humans and is a bio-terrorism agent or is a naturally occurring event.”

“It gives pharma and scientists generally much better tools to understand bacteria and then manipulate them, hopefully for peaceful purposes.”