Since the first Deep Brain Stimulation initiative of Tsinghua University in 2000, PINS Medical has gradually established a multinational corporation with headquarters based in Beijing and an international business center in Singapore. As an innovative high-tech enterprise with a focus on neuromodulation, a variety of clinical products have been developed to date, which include stimulators for deep brain, vagus nerve, spinal cord and sacral nerve stimulation therapies. PINS Medical devotes itself to providing cutting-edge treatments for patients who suffer from neurological disorders such as Parkinson’s Disease, Epilepsy, Chronic Pain and OAB, etc.

As part of the “National Engineering Laboratory for Neuromodulation”, PINS Medical works in close cooperation with Tsinghua University and the numerous affiliated clinical centers, becoming a center of attraction for a wide range of professional talents in areas of clinical research, innovative R&D and business management. Since 2008, PINS Medical has developed rapidly in becoming a leading brand in neuromodulation within the Chinese market, due to the success of its creative research platform that efficiently links basic research, R&D of novel products, clinical testing and market entry.

With an outstanding reputation as a high-tech healthcare corporation, PINS Medical has a primary mission for providing innovative, high-quality products and services for patients to improve quality of life. PINS, which stands for Programmable Implanted Neuromodulation Stimulator, is also an abbreviation of “Patient Is No.1 always”. This clearly presents the goal of PINS Medical for “restoring hope”, not simply as an innovation company but also across society to citizens.

Looking into the future with the continuous rise in incidence of neuropsychiatric disorders and increased social burden across the globe, PINS Medical along with local governments, research centers, companies and top academic scientists, are now developing and promoting innovative therapies worldwide.

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Best of both worlds: Next-generation sequencing in frozen and FFPE tissue

Clinical tissue samples come in many forms, and some are easier to analyze by nucleic acid sequencing than others. There are two popular forms of sample preservation: fresh-frozen and formalin-fixed paraffin-embedded (FFPE). In short, it’s easier to sequence fresh-frozen samples than FFPE ones, but FFPE tissues can be stored for longer and at ambient temperatures. New technology, however, accurately analyzes the nucleic acids in both kinds of samples.

Scientists started fixing samples in formalin in the late 1800s. As a result, there are now millions of extant FFPE samples around the world, which represent an invaluable collection of potential information about disease—especially cancer, because virtually every kind of tumor can be found in this sample format. Despite this gigantic clinical resource, much of it has long remained unreachable through sequencing analysis, because FFPE samples of cancer tissue include only small amounts of low-quality nucleic acids (1).

Until just a few years ago, microgram quantities of purified DNA or RNA were required for next-generation sequencing (NGS) profiling. However, that has changed. “Recent advances have enabled the preparation of high-quality NGS libraries from just tens of nanograms of material, including degraded samples with fragment sizes of less than 100 base pairs,” says Kevin Meldrum, vice president of product development at Illumina, a biotechnology company headquartered in San Diego, California. “Genomic profiling can now be utilized across a broader set of samples and on a more routine basis,” he says, and it can be applied equally effectively to both fresh-frozen and FFPE clinical samples, both with traditional mechanical fragmentation, and more recently with advances in enzymatic fragmentation, such as Illumina’s Nextera™ Flex for Enrichment kit.

Viewing variants

Using whole-genome sequencing (WGS), scientists can sequence the entire genome of an organism; or with whole-exome sequencing (WES), they can choose to sequence only the nucleic acids that are transcribed to RNA. “The key clinical applications of WGS and WES are the discovery of pathogenic variants,” says Pauline Robbe, NGS expert at the University of Oxford in the United Kingdom.

When dealing with clinical samples, DNA sequencing can be applied in many ways. In the case of rare genetic diseases and types of hereditary cancer, comparing sequences of a person with the disease and a family member without it can identify the disease-related mutation. A well-known example involves the BRCA (BReast CANcer) genes and female breast cancer. “In the case of sporadic cancers, the oncologist wants to identify variants present in the cancer cells—and not in the normal cells of a person—which lead to defects in one or several genes,” Robbe says. Performing WGS/WES on normal and cancerous cells can provide valuable data. “This information will guide the clinician in the diagnosis—in subtyping and grading the cancer or identifying the tissue of origin of a metastasis—or in treatment, by giving a drug that will take advantage of these mutated genes.”

These sequencing applications can be challenging. If a fresh-frozen sample includes a large proportion of healthy cells relative to tumor cells, sequencing it in bulk can miss crucial mutations. Archiving samples through an FFPE process preserves the tissue morphology, but degrades the DNA and RNA, increasing the difficulty of the sequencing analysis and reducing its accuracy. To determine the quality of DNA samples, Robbe uses Illumina’s Infinium™ FFPE QC Kit. For damaged DNA, Illumina’s TruSight™ Oncology UMI Reagents use unique molecular modifiers (UMIs) that can be combined with computational analysis to improve sequencing accuracy.

Another issue can arise when researchers are working with RNA and want to study only messenger RNA (mRNA)—ribosomal and transfer RNA can contaminate their sample. In such cases, Meldrum suggests using Illumina’s TruSeq™ RNA Exome Kit. “It allows researchers to interrogate mRNA using a capture approach that avoids contamination by other RNA species,” he explains. “This method is also compatible with nucleic acids derived from fragmented FFPE samples.”
Decoding the immune system

To understand disease and how the body fights it, scientists are currently studying the immune system. At Cofactor Genomics, they precisely characterize the immune cells in FFPE samples. “This is informative for understanding cancer,” says chief operating officer Dave Messina. “For example, immune characterization of a sample can be used to predict a tumor’s response to chemotherapy.”

To characterize the immune cells in tumor samples, workers at Cofactor Genomics first use RNA sequencing (RNA-Seq) to acquire hundreds of signals of pure immune-cell populations, then place them into computational models they call Health Expression Models. “We’re taking advantage of modern computational techniques to integrate lots of signals into a robust model of something as complex as immune cells,” Messina explains. “We pair that with molecular technology to get reproducible readouts even from challenging clinical samples.” Using this multidimensional approach enables Cofactor to quantitatively measure immune cells in complex mixtures with high sensitivity.

Scientists can take advantage of this technology through Cofactor ImmunoPrism™, an immune-profiling kit that works with Illumina sequencing platforms. “In particular, this combination provides a clear readout of what immune cells are doing in the tumor microenvironment,” says Messina, who notes that ImmunoPrism™ can also be used with fresh-frozen or FFPE samples. In addition, Cofactor Genomics offers research-use and clinical-use versions of the platform, and the latter have been approved under the company’s CAP-CLA license.

Hunting down heterogeneity

To deal more precisely with cancer, both in diagnosis and treatment, scientists must study tumors more carefully. “Historically, people did bulk testing—taking a general tissue sample and processing it,” Meldrum says. “Now, we have techniques to isolate single cells from tissues and profile those cells individually for a higher-resolution view at a cellular level to identify mutations.”

There’s good reason to delve into cancer at the single-cell level. “A substantial proportion of tumors consist of genotypically distinct subpopulations of cancer cells,” according to Jorge Reis-Filho and colleagues at the Memorial Sloan Kettering Cancer Center, in New York City, New York. “This intratumor genetic heterogeneity poses a substantial challenge for the implementation of precision medicine” (2).

Reis-Filho’s team used Illumina library preparation and multiplex sequencing to analyze FFPE breast-cancer samples. Their study produced similar results when interrogating gene copy number in fresh-frozen and FFPE samples. The single-cell profiling that single-cell profiling to “dissect the genetics of histologically or phenotypically distinct cancer components, and trace their evolutionary history.”

From heterogeneity to harmony

The ability to work with FFPE samples will dramatically increase the amount of clinical sequencing information produced—which will in turn create a series of data challenges. NGS data, for instance, drives three levels of analysis. Primary analysis consists of identifying the bases in the raw read of a sequence, a function built into each sequencer. Secondary analysis differentiates the bases in an analyzed sample from a reference sequence, and identifies genomic variants. Various algorithms—such as DRAGEN (Dynamic Read Analysis for Genomics)™, developed by Edico Genome, which is now owned by Illumina—exist for this process. “DRAGEN™ accelerates this analysis with hardware and software, reducing whole-genome variant calling from hours to 15 or 20 minutes,” Meldrum says.

Finally, tertiary analysis interprets the significance of the bases and variants in a sequence. “There are references and databases that you can ping to see if the variants are important,” Meldrum explains.

To make the most of this collection of heterogenous data, companies must harmonize their data formats. “There are a couple of community forums underway,” Meldrum says. For example, Illumina is collaborating with the Broad Institute in Cambridge, Massachusetts, to use its Genome Analysis Toolkit (GATK). “We’d like to make sure that our algorithms are compatible with GATK,” he points out.

There are many good reasons to make the effort needed to drive this kind of teamwork. As Meldrum says, “These advancements enable cancer researchers to utilize a broader range of NGS-based profiling techniques on precious clinical and archival samples, moving beyond targeted assays that generate data of variable quality.”

References
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