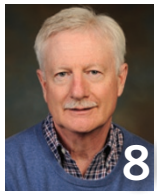
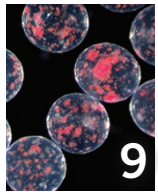
Serious series:
Biotech startups are landing huge Series A funding rounds



Higher proof:
NIH alcohol chief promises to integrate addiction research



Aye islet:
Capsules protect transplanted islets from immune attack

Revved-up epigenetic sequencing may foster new diagnostics

The promise of epigenetic therapy has captured the imagination of the biomedical field ever since 2004, when US regulators approved Vidaza (azacitidine). The drug, manufactured by New Jersey–based Celgene, is a chemical analog of the cytosine nucleoside used in DNA and seems to treat blood-related diseases known as myelodysplastic syndromes by modifying the epigenetic elements of genes involved in regulating the cell cycle. But only a handful of such therapies have made it to the market in the decade that has followed, in part, researchers say, because it remains difficult to efficiently decipher where and how molecules known as methyl groups leave their epigenetic mark on a particular gene.

One limitation of many epigenetic analytical methods is that they provide only the percentage of base pairs in a given sample that have methyl groups attached, rather than the specific locations of those modifications. Whole-genome sequencing can yield more precise methylation maps, but these tests cost thousands of dollars and can take weeks to complete.

Now, several innovations described in recent months could allow researchers to find where methyl groups lie on specific genes more cheaply and more quickly than this process usually requires—an essential advancement if researchers are to determine the cause of certain life-threatening diseases and develop drugs that can suppress these gene-silencing groups. "There is some hidden information that is not yet being captured," says Paul Soloway, a biochemist at Cornell University in Ithaca, New York, who works on technologies for epigenetic profiling. "So, it's important to think ahead and try to break down current barriers."

One example comes from Roche NimbleGen, a Wisconsin-based division of the Swiss pharmaceutical giant Roche that is building a machine that can detail the epigenetic modifications on short fragments of DNA. At the American Society of Human Genetics annual meeting in Boston in October, the company unveiled a new method called SeqCap Epi that can generate the same high-resolution data that one can obtain from whole-genome epigenetic analysis but for smaller targets ranging from 10,000 to 75 million base pairs in size. According to Daniel Burgess, a senior scientist at Roche NimbleGen, this provides an inexpensive way of capturing epigenetic data in a high-throughput fashion for researchers who might only be interested in a subset of the genome. "We have the only practical method for making sufficient probes for targeted enrichment," he says.

"The general idea is innovative," says Xian Chen, a biochemist at the University of North Carolina at Chapel Hill. "The fact that you can handle a significantly higher number of samples to achieve power is vital for human studies," adds Paula Desplats, a neuroscientist at the University of California–San Diego. According to Burgess, the SeqCap Epi system could hit the consumer market as early as this month.

Probing advances

Some researchers also seek to characterize the epigenome not through sequencing but through functional analysis. This tactic capitalizes on the fact that DNA, which is wound up with protein in chromatin complexes, becomes silenced when it binds to methyl groups.

Roche NimbleGen

Swift and nimble: Roche NimbleGen's SeqCap Epi.

For example, Bradley Bernstein and his colleagues at the Massachusetts General Hospital in Boston recently developed a way of altering epigenetic marks by coupling customizable DNA-binding domains called transcription activator-like effectors, or TALEs, with the enzyme lysine-specific demethylase, which can remove certain methyl groups. Working in a leukemia cell line, the researchers used the chromatin-modifying constructs to shut off specific methylation enhancers—short regions of DNA capable of increasing gene expression. This allowed Bernstein's team to map the epigenetic marks that control these important functional genetic elements.

"You now have an opportunity to correct [epigenetic] alterations and ask what the consequences are," says Bernstein, who described the method, dubbed 'locus-specific chromatin editing', in the December issue of *Nature Biotechnology* (**31**, 1133–1136, 2013). He adds that this is particularly important in cancer or autoimmune diseases where chromatin changes correlate with disease. Others are enthusiastic, too: "This type of tool makes a big stride in the field," Desplats says.

Although these advances give hope to geneticists, they also lament that the epigenetic changes in DNA vary from one cell population to the next within the same organism. That has led Soloway and his Cornell colleagues to begin developing an approach called 'single-chromatin molecule analysis at the nanoscale', or SCAN. The method works by staining chromatin with a fluorescent dye to which antibodies are bound. These antibodies affix to epigenetic marks on DNA, allowing researchers to note the degree of fluorescence and to determine the general amount of epigenetic changes that are present in a cell population. So far, Soloway's team has used the technology to analyze molecules in various human cell populations, including stem cells and cancer cells. They found different patterns of methylation in normal cells compared with tumor-forming ones (*Proc. Natl. Acad. Sci. USA* **110**, 7772–7777, 2013).

Trey Ideker, a molecular biotechnologist at the University of California–San Diego, thinks this kind of approach is the logical next frontier for epigenetic studies. "We can already do single-cell DNA and mRNA sequencing," he says. Thus, "it seems quite natural that single-cell epigenetic analysis would be the next domino to fall."

Arielle Duhaime-Ross