THE AUTHOR FILE

Peter Lansdorp

Zeroing in on single DNA strands

Assault is an everyday occurrence for the body. DNA is badgered by background radiation, chemicals or run-of-the-mill cellular processes. Thankfully, damage from these daily attacks is usually repaired, says Peter Lansdorp, who has an MD from Erasmus University in Rotterdam and a PhD in experimental hematology from the University of Amsterdam. "Interestingly, some cells seem to be better protected than others," he says. He wonders how cells differ in their repair capabilities and if the accumulated damage contributes to age-related decline in cellular function.

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Lansdorp pursues these questions in labs in two countries. He has appointments at the University of British Columbia and the BC Cancer Agency in Vancouver, Canada. This February, Lansdorp was also invited to set up the European Institute for the Biology of Ageing at the University of Groningen in The Netherlands, where he grew up. It was an offer in the 'once-in-a-lifetime' category, he says. In each of his labs, he plans to put to work a new method called Strand-seq, which reveals facets of the genome that traditional sequencing cannot, such as certain rearrangements after DNA breaks occur.

During cell division, when the two strands of the double helix zip apart, information is occasionally swapped between strands on different chromosomes. Increasing levels of such exchanges—a hallmark of DNA damage and cancer—can evade traditional genome sequencing.

With Strand-seq, Lansdorp and his colleagues could sequence single strands of DNA and detect a cell's first signs of genomic stress and instability. The approach finds a way to capture information from one strand of DNA, a parental template that acts as a kind of generational time capsule. Strand-seq lets researchers perform single-cell sequencing of the parental DNA template strand.

The sequencing itself must occur in replicating cells at a precise time in the cell cycle: right as the parental strands separate into daughter cells and the strands are forming new DNA double helices.

The team separates parent and daughter strands by labeling newly synthesized DNA in dividing cells with a chemical called bromodeoxyuridine (BrdU). The chemical's presence allows the researchers to target and degrade the new strands in the daughter cells while leaving the parent template strand intact. In a following step, the scientists pull out the parent template strand and sequence it.

One major advantage of the method is that it provides the orientation of the sequence. In current approaches, when DNA from a single cell is amplified and sequenced, directional information is lost, Lansdorp says. That loss makes it much harder to detect genomic rearrangements. With Strand-seq, it is possible to see when DNA sequences are flipped or swapped during cell replication.

As an added surprise, the team found that by using Strand-seq on mouse cells, they could detect misoriented fragments in the mouse reference genome that together add up to a surprising 1% of the genome.

When the project began, the team set out to create a sequencing library with a single cell's meager 6 picograms of DNA. "Most people would think that is not reasonable or possible," he says. His team is exploring how to technically ease the task of making such libraries from single cells.

Previously, standard cytogenetic techniques showed mouse embryonic stem cells to have around eight recombination events, also called sister chromatid exchanges, per cell. The team confirmed those findings but also discovered that some cells have many more exchanges and some have none, he says. "The variation in the frequency of these events is interesting. What does it mean?" Probing whether some of these cells have better damage repair processes than others or why they may not be sustaining as much damage is unexplored territory, he says.

> "Interestingly, some cells seem to be better protected than others."

In many ways, Lansdorp feels the method opens new venues for exploration, with the potential to ultimately translate findings into approaches that help prevent or treat disease. The work also reaffirms his choice to become a researcher and not a physician, a decision he made as his medical training drew to a close.

Lansdorp's dedication to research fuels his travels back and forth between his labs to explore these new areas, and he focuses on supporting his teams by staying in touch via videoconferences. "My Vancouver lab is very mature, with excellent people like Ester Falconer, who spearheaded the development of Strand-seq," he says.

Vivien Marx

Falconer, E. *et al.* DNA template strand sequencing of single cells maps genomic rearrangements at high resolution. *Nat. Methods* **9**, 1107–1112 (2012).