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Stem Cell Crusader Offers Hope in Battle Against Neurological Diseases

At the Scripps Research Institute, Jeanne Loring is using induced pluripotent stem cells to reverse the effects of Parkinson's disease, multiple sclerosis, and more. She trusts her vital RNA-seq analysis to the Maverix Analytic Platform.

Jeanne Loring isn't just a pioneering stem cell biologist. For millions of people dealing with Parkinson's and other neurological diseases, she may be something of a personal hero.

Loring, a professor of developmental neurobiology and director of the Center for Regenerative Medicine at the Scripps Research Institute, has presented some of the earliest data suggesting that cell replacement therapy based on induced pluripotent stem (iPS) cells may reverse the progression of Parkinson's disease. Using a rat model, her team demonstrated that the transplantation of dopaminergic neurons formed from patient fibroblasts sent the disease into a hasty retreat, dramatically improving the rats' health.

The Loring group plans to go to the FDA next year to begin clinical trials. If treatment in humans parallels what they saw in rats, Loring says, this cell replacement therapy could "set the clock back about 30 years" for patients with Parkinson's disease. That might sound pie-in-the-sky coming from another scientist, but Loring is known throughout the community for her commitment to quality control and precision — so people are taking notice.

The Parkinson's project is just one of the many seemingly impossible challenges tackled by the 20-person Loring lab. The common threads are stem cell biology and genomics, fields Loring has worked in since graduate school. Though her lab is based at a research institute, she combines genomics with translational research to ensure that these projects have utility far beyond the bench.

Her team is making the transition from RNA microarrays to single-cell RNA sequencing. In the process, they discovered Maverix Analytic Platform and adopted it for their RNA-seq analysis pipeline. Relying on Maverix lets anyone on the Loring team dive into RNA-seq results, regardless of how much bioinformatics background they

Jeanne Loring, Professor, Scripps Research Institute

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have. It also frees up lab members to do other important work while the platform automatically crunches data for them.

Fantastic iPS Cells

Loring's use of iPS cells is the latest of many attempts to realize the promise of stem cells. "I've evolved to use the stem cells of the moment," says Loring, who has also worked with neural crest stem cells, mouse embryonic stem cells, and a host of other versions. When iPS cells — or mature cells that have been treated with a cocktail of transcription factors to revert to their pre-differentiated, pluripotent state — first came on the scene, Loring was skeptical. Was it really possible to convert adult cells into ones that resembled stem cells, and then to expect them to behave like natural stem cells?

"I didn't believe it," she recalls. "I had to prove it to myself, and by now I've proven it to myself about a thousand times. It's a fantastic technology." Loring's team has spent years analyzing these iPS cells and comparing them to naturally occurring stem cells. "We have found that they are perfectly fine and very much like embryonic stem cells," she says.

By way of proving the iPS cells' value to herself, Loring developed what is now the community's most commonly used method for qualifying pluripotency in these cells. The freely available tool, called PluriTest, has been used thousands of times to perform quality control screening on thousands of iPS and embryonic stem cells. Originally designed for microarray data, the Loring team is revamping PluriTest to work with RNA-seq data as well. "It's the first example of the many in vitro diagnostic tests we're developing for quality control," she notes.

The switch in technology platforms is characteristic of Loring's commitment to generating the best data for these cells. "We want to use a platform-independent method, so we're turning to mRNA-seq for quality control, for being absolutely certain we have the same cells every time — especially if we're going to be putting them into people," Loring says.

Having that kind of data matters when you're working on high-stakes projects focused on Parkinson's, multiple sclerosis, and Fragile X syndrome, among others. The Parkinson's effort is furthest along, with Loring already hoping for FDA approval to perform clinical trials based on the positive results from her test in rats. The lab takes skin cells from patients with the disease and uses the established protocol to coax those cells back into an undifferentiated state. These iPS cells are guided to develop into dopamine neurons, the type of cell that's killed off as Parkinson's progresses. The idea is to transplant these cells back into the patient's brain to replace the neurons that have died off with onset of the disease. Because the cells originally come from the patient, rejection risk is minimized. A single treatment, Loring believes, could be enough to ward off symptoms for the rest of that person's life.

In addition to this groundbreaking work with Parkinson's, Loring recently gave hope to millions of patients with multiple sclerosis when her lab used iPS cells to treat mice paralyzed with that disease; within weeks, the mice were walking again. Loring's lab has used RNA-seq to identify a critical cell type among MS patients, which is important for choosing a therapy approach. For Fragile X syndrome, the team is doing in vitro work to get individual cells to a state where they can be used for drug screening. Funding for her lab has been provided by the California Institute for Regenerative Medicine, philanthropic donations, and the NIH.

Throughout the RNA-seq work associated with these experiments, the team uses Maverix Analytic Platform for analysis of the data. In the Parkinson's project, for example, Loring's lab has to characterize cells when they're first made into iPS cells; at the midpoint of development to ensure proper differentiation; and again at the end of the 25-day cycle as a quality control step before transplantation. Each time, they turn to Maverix to assess the transcriptome of these valuable cells.

Biologists and Bioinformatics

Long before her introduction to Maverix Biomics, Loring worked at Incyte Genomics in the heyday of the Human Genome Project. There, as the lone biologist among bioinformaticians, she saw firsthand the differences in skill sets and the communication challenges that existed between people with a biology background and those with a computational background. In her lab, Loring requires that everyone do bioinformatics work to make sure the predominantly biologist group is familiar with data analysis.

That doesn't mean she expects them to become advanced coders, which is where Maverix comes in. "With Maverix, the data are already analyzed so it doesn't take a bioinformatics genius to interpret the data once we get it back," Loring says. She began using the tool recently as it became clear that her lab didn't have the bandwidth to perform advanced RNA-seq analysis on its own. "When we tried out Maverix, we were impressed," she says. "We decided that it was more cost-effective and probably more reliable to work with Maverix than to do it internally."

Her team likes being able to compare results from two different analysis pipelines within the Maverix Analytic Platform, which integrates standard methods with best-in-class analysis tools such as TopHat, STAR, Cufflinks, and DESeq as well as its own version of the UCSC genome browser. What Loring likes is the time savings: "Using Maverix doesn't take up time that my postdocs and graduate students could be using to develop new things," she says. "And it's not just the time of performing the analysis; it speeds up the learning curve for the

people in the lab who don't have bioinformatics experience." Indeed, one of her biologists is using the platform to learn bioinformatics for the first time.

Another key feature is the ease of sharing data in a collaboration. Loring's team is working with a scientist in Germany, and being able to share the data online from Maverix "is much simpler than trying to convey the data from my lab to him," she says. "We can both look at the data simultaneously, which is really helpful."

Loring says the speedy turnaround time for getting results, frequent improvements to the software, and presentation of the data are other advantages of the platform. "Data appears the way you expect it to be; it's in a common format, which is really important," she says. "mRNA-seq is not a trivial thing to deal with."

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