Devices aim to deliver on stem-cell therapies

Bendable needle increases reach of a single injection to the brain.

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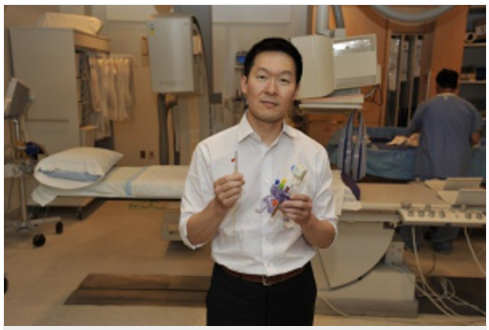
As the surgical team prepared its instruments, a severed human head lay on the plastic tray, its face covered by a blue cloth. It had thawed over the past 24 hours, and a pinky-sized burr hole had been cut near the top of its skull. Scalp covered with salt-and-pepper stubble wrinkled above and below a pink strip of smooth bone.

Over the next two hours, the head would be scanned in a magnetic resonance imaging (MRI) machine as the researchers, led by Daniel Lim, a neurosurgeon and stem-cell scientist at the University of California, San Francisco, tested a flexible needle for delivering cells to the brain.



J. Bardi/UCSF

Neurosurgeon Daniel Lim's injection system can bend sideways, delivering therapeutic stem cells to the brain through fewer holes in the skull.

Several laboratories are investigating ways to treat neurological diseases by injecting cells into patients' brains, and clinical trials are being conducted for Parkinson's disease, stroke and other neurodegenerative diseases. These studies follow experiments showing dramatic improvements in rats and mice. But as work on potentially therapeutic cells has surged ahead, necessary surgical techniques have lagged behind, says Lim.

In 2008 researchers led by Steven Goldman at the University of Rochester in New York showed that they could make severely disabled mice able to walk by injecting human glial progenitor cells into five sites in the rodents' brains.

Those results are encouraging, but a human brain is more than 1,000 times larger than a mouse brain, and delivering cells to the right places is much harder. "People know how to get cells into animals but forget about the scale-up problem with humans," Lim says.

Necessary tools

Working with bioengineers and neurosurgeons, Lim designed a needle that bends. First, a straight, thin tube is injected into the brain and a flexible nylon catheter pushed through it. A deflector inside the tube arcs the catheter up and away from the entry track, and an even narrower plunger ejects cells from the catheter. In one injection, the device can deposit cells anywhere within a 2-centimetre radius along the track, a volume bigger than an entire mouse brain.

Several researchers hope to use Lim's device for clinical trials in brain cancer and neurodegenerative disease. Xianmin Zeng, a stem-cell scientist at the Buck Institute in Novato, California, who worked with Lim to test the device on swine, says she hopes to file an application to

use the device in clinical trials for Parkinson's before the end of 2014.

A team of scientists from UCSF and StemCells, a biotechnology company based in Newark, California, wants to use the device to treat Pelizaeus–Merzbacher disease, a deadly neurodegenerative disorder. Last year, the company reported promising results from a phase I clinical trial testing neural stem-cell transplants for treating this disease.

Track to improvement

Lim's device could cut down on the number of injections required for cell treatments, says Zeng. It could give more precise control of the volume of cells delivered and ensure that the cells delivered into the brain stay in the brain, avoiding the problem of reflux, in which cells injected using straight needles flow back out to the brain surface along the needle's path.

"Every time you put a needle into the brain, you run the risk of a hemorrhage and raise the risk of unwanted effects," says Ian Duncan, a neuroscientist at the University of Wisconsin–Madison, who is not involved in Lim's project.

Also, unlike other needles used for cell therapies, Lim's device contains no ferromagnetic metals and so is compatible with MRI. The imaging would enable researchers to monitor patients for signs of hemorrhaging and to combine cell therapy with other techniques, such as depositing electrodes for deep brain stimulation, an experimental therapy for Parkinson's disease.

But these potential advantages require the needle to work as hoped. Lim and his colleagues have experimented with the needle in agarose moulds and live pigs, but they began testing the device and the surgical workflow with real human tissue last week.

The tests were largely successful. The researchers verified that the device can be mounted stably to the skull, and that injections take only a few minutes and go to the anticipated place. There was one hitch: when the device was mounted on the skull, some of its calibration markings were hard to read, but Lim says this will be easy to fix.

Even so, Goldman anticipates that simple, straight needles will still be used for therapies in the next several years. He is part of the Empire State Stem Cell Board, a consortium that received US$12 million last year to bring a stem-cell therapy for multiple sclerosis to clinical trials. Goldman thinks that the cell type he is working with could travel far beyond where they are placed with a needle. "They really zip along quickly," he says.

Lim's needle is not the only new brain-injection device being tested for human use. Ivar Mendez, a neurosurgeon at Dalhousie University in Halifax, Canada, has created the Halifax Injector, which delivers cells not by a manually controlled syringe by tiny computer-controlled motors. Up till now, Mendez says, "The way the injection has been done was with very primitive systems."

There's no question delivery will be important, but solving that problem will require better a better understanding of how cell therapies in the brain work, says Gary Steinberg, chair of neurosurgery at Stanford University in Palo Alto, California. "We still don't know what cell type," he says. "We don't even know if direct-to-the-brain is the right route of administration." Each disease, injury, and cell type poses new sets of issues, he says.

But Lim worries that efforts like his are already behind, given the state of advancement in the development of new therapies. "If we don't do the work now before we think we need it, then it will never be ready."

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- Clarifications

Clarified: An earlier version of the article stated, in reference to using the device to treat Pelizaeus–Merzbacher disease, that UCSF and StemCells scientists "hope to get regulatory approval to do so by the end of the year". StemCells is currently not involved in clinical trials needed for approval of device, but the device might be incorporated into future trials, pending US Food and Drug Administration clearance known as 510(k).

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