Q&A

UCI STEM CELL RESEARCH CENTER

Aileen Anderson: Bridging the gap

The potential to use stem cells to restore a spinal cord damaged by injury or disease holds irresistible allure. But repairing this seemingly simple circuitry has proved much more complicated than most people anticipated. Neuroscientist Aileen Anderson, who directs the Sue & Bill Gross Stem Cell Research Center at the University of California, Irvine, spoke to *Nature* about where the field stands.

How could stem-cell therapy help someone with a spinal-cord injury?
Around one-third of all US spinal-cord injuries are complete, which means that motor instructions coming down from the brain cannot cross the site of injury to the muscles, and sensory information from below cannot reach the brain. So if you have a mid-thoracic spinal-cord injury, you've disrupted not just sensory and motor function at that level — which in this case would affect the chest and abdomen — but also the signals that flow through it, such as those to and from the legs.

People have long thought we should be able to patch that gap in the circuitry — just replace the cells that are lost and provide a path for signals to flow again. It looked like a straightforward way to intervene.

How straightforward has it been to put into practice?
As a field, we've made tremendous progress. We can use stem cells derived either from fetal tissue or from adult cells, or we can use more differentiated precursors specific to cells in the central nervous system, and we can test them in both animal models and clinical trials. But we've also learnt that the human spinal cord is much more complicated than we would like it to be. Growing and transplanting cells is not enough — they have to survive and they have to integrate, and we are not good at getting them to do that yet.

We also now know that there might be different ways to repair the spinal cord. Growing circuitry to bridge the injury and connect the axons below it with those above is just one option. Most people with a spinal-cord injury (even if that injury is complete) have a contusion injury. That means the cord is crushed, rather than cut, and some axons at the injury site are spared. So another way to restore function might be to improve the circuitry that is still there. You could boost neural transmission by improving the insulation of the remaining axons, for instance. Or you could try to modulate inflammation to encourage a pro-regenerative state. There could be lots of ways to improve function, and different approaches involve different stem-cell populations. Right now, no single cell or pathway stands out as the best solution.

What have you learnt from clinical trials?
Enough trials have gone forward already that we know the safety profile is good, the tolerability has been good, and there have been inklings of potential for improvements in recovery of function. That all looks very promising. But we have a couple of additional issues.

One is the enormous variability in the injuries that people sustain: what area of the spinal cord; what functions are most affected; and how large the injury is. That's the last thing you want in a clinical trial — you want all of those factors to be replicable. So a really crucial thing is to intelligently and tightly stratify potential participants, so that you're selecting people for trials who are most likely to benefit from the therapeutic that you're trying to test.

There's also the problem that some people experience spontaneous recovery from spinal-cord injury, and in a small trial it's nearly impossible to separate true functional repair from happy coincidence. The field is going to struggle with that until we get to larger-scale clinical trials, but we can't do multiple 600-person clinical trials every year — we just don't have a large enough number of participants available. There's also a risk that a bunch of failures in short succession will put off patients and potential commercial partners in the future. So when we're thinking about running clinical trials, we really need to think carefully about what kind of cell therapies have the greatest chances of success, in what groups of people, with what endpoints, and target them as closely as possible.

Where does your work fit into this?
We're trying to understand how much variation there is between stem-cell lines. When you're working with cell therapeutics and moving towards a clinical trial, you have to be able to measure the identity, purity and potency of the cells you're using. You have to know that the cells that you've tested in animal models will have the same effects when you give them to people. We've tested ten cell lines, and have found huge variation in whether lines yield functional repair or not. So even if you think you have the same thing, if it's a different cell line, it's not necessarily going to have the same effect.

With so many unknowns, are we really ready for trials in people?
There's debate in the field about that. Do you need to know and understand everything before you move into the clinical setting, or do you just need to take the plunge and see whether we can make people better?

I think we need to continue to go forwards with small, really well-controlled and well-designed phase I and phase II trials that can test different cell types and validate early outcome measures, because animal work provides limited information. The circuitry is fundamentally different in humans and rodents, so I think there's increasing recognition that we're going to have to go ahead and do the human experiments.

It's easier now because we know that you can do clinical trials in people who are living with spinal-cord injury and deliver a cell therapeutic to the spinal cord without making their situation worse. That was everybody's big fear, but fortunately it's not been realized. That's extremely encouraging because, at the end of the day, we need to put human cells into humans to understand what's going to happen.

Interview by Lauren Gravitz
This interview has been edited for length and clarity.