Regenerating hope

H igh-profile support from celebrities like Christopher Reeve, who suffered a spinal cord injury in 1995, has helped to focus media attention and financial resources on research into spinal cord repair. A television commercial aired in 2000 used digital trickery to show Reeve walking across a stage in the not-too-distant future—a clear statement to the scientific community and the world that Reeve and other spinal cord injury patients were hoping for a miracle.

Although scientists have been able to produce substantial functional recovery in animal spinal cord injury models, no revolutionary advances have yet reached the clinic. Understandably, patient groups have been vocal in their frustration with this apparent slowness. Reeve himself has been openly critical, suggesting that scientists need to take bigger risks if they hope to provide real progress. Repairing the injured spinal cord is no easy task, however, and rushing to bring preliminary approaches into clinical practice may do more harm than good.

Basic researchers have made substantial progress in determining what factors interfere with healing after spinal damage in adults. When the spinal cord is injured, axons are severed, immune cells fill the lesion site, and local astrocytes eventually form a ‘glial scar’. Regeneration of damaged axons is hindered by their limited growth potential, by the glial scar, and by a variety of inhibitory molecules in the surrounding myelin (as two papers in this issue discuss). Oswald Steward, who studies spinal cord injury at the University of California Irvine and heads the Reeve-Irvine Research Center, calls it a “sea of nastiness”. To a regenerating axon trying to traverse the lesion, it might as well be a brick wall.

In spite of this increased understanding, however, few potential treatments have completed clinical trials in humans. Of these, one of the most promising is the synthetic corticosteroid methylprednisolone. Given within hours after injury, it seems to limit the amount of cellular damage and improve neurological recovery. Other potential treatments are currently in clinical testing or soon may reach that stage. They use a variety of approaches from boosting the function of immune cells within the lesion to promoting regeneration of severed connections by making the surrounding tissues less inhibitory to growth.

Regrowth of severed axons into their original circuits may not be the only way for patients to regain function. Because most spinal cord injuries in humans do not cause complete cord separation, researchers are also looking at ways to enhance the function or sprouting of intact pathways that might be able to compensate for those that were lost. For example, work from Bareyre et al. in this issue shows that severed axons can bypass the lesion by forming contacts onto intact propriospinal neurons to create a new spinal circuit.

Finally, not all approaches are drug-based. Some research suggests that neural circuits can turn off when not used for long periods of time (‘learned non-use’), but might be able to be reactivated by intense rehabilitative training. Reeve is a proponent of such approaches and has regained some function through various types of training.

Many in the scientific community remain cautious about the promise of these drug-based and rehabilitative approaches to produce meaningful recovery in spinal cord injury patients. A major problem, explains Fred Gage of the Salk Institute, is that the field is full of studies that have claimed recovery in animal models, but have been difficult to reproduce. Some of this inconsistency is likely due to differences in technical methods or injury models, but Gage feels that in many cases, researchers do not understand enough about the underlying mechanisms to ensure the reliability and reproducibility of their approaches. Spinal cord injury is a complex, multi-faceted problem, and thus is not likely to yield to a simple cure.

Another problem with bringing new research findings into clinical use is economic. Academic laboratories generally do not have the funds or facilities to translate basic science into potential therapeutic strategies. Various groups have been working to remove these barriers. For example, the US National Institute of Neurological Disorders and Stroke has developed funding initiatives geared toward promoting translational research in spinal cord injury. The agency also offers help with clinical trials. Program Director Naomi Kleitman hopes such initiatives will speed the pace of translation to the clinic and encourage new investigators to enter the field. Foundation-supported institutes, such as the Reeve-Irvine Research Center headed by Steward and supported in part by the Christopher Reeve Paralysis Foundation, also provide dedicated staff and facilities to help test and develop new therapies.

Are scientists being too timid when it comes to trying ‘risky’ approaches? Arthur Caplan, a bioethicist at the University of Pennsylvania, thinks not. He feels that several factors guide the way scientists view risk. First, much of what scientists are or are not able to do is dictated by society, in the form of laws and regulations. In addition, many new approaches fail, and scientists are wary of building false hope in patients with treatments that have not been sufficiently tested and replicated by others in the scientific community. “Patients often don’t understand replicability,” says Caplan. Some patients feel that taking the risk is better than doing nothing, but Caplan argues that there is a third option many people do not take into account: undergoing a risky procedure may do more harm than good. “We could end up killing you faster, or turning you into a vegetable,” he warns.

Although researchers understand patients’ desire for more rapid progress, most feel that investigators are being appropriately cautious. Many agree with Stephen Strittmatter, who studies spinal cord regeneration at Yale University: “Scientists are working as fast as they can.”