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Towards therapy for spinal cord injuries

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The Fifth International Spinal Research Trust (ISRT) Research Network Meeting was held on 6–7 September 2002 in London.

ISRT Network meetings have the enviable reputation of providing a forum where all those involved in spinal cord injury (SCI) research – from clinicians, to internationally renowned scientists, to research students – can discuss all aspects of their research. ISRT grant awardees and invited speakers presented data at the fifth Network Meeting, with the valuable discussion periods timetabled into the meeting helping to further endorse this reputation.

In his opening address, Lord Sainsbury, the UK Minister for Science and Innovation, emphasised the role of the ISRT in advancing research that could revolutionise prospects for the $\sim$2 million people who live with SCI. Acknowledging that Government funding will never be sufficient to fully fund the necessary work, he praised the pioneering role of the ISRT in instigating the Research Network and the Clinical Initiative, commenting that 'together, these activities will ensure that patients with SCIs will receive effective treatments as soon as possible'. Professor James Fawcett, Chairman of the ISRT Scientific Committee, then highlighted several likely therapeutic opportunities, including preventing inhibition by blocking either Nogo or chondroitin sulphate proteoglycans, stimulating growth using either growth factors or manipulating intracellular-signalling pathways, and bridging lesions using either olfactory glia or embryonic spinal cord. Each of these was discussed at more length throughout the meeting.

Neurons in the embryonic spinal cord regenerate much better than those from the adult spinal cord. The decrease in regenerative ability coincides with the formation of CNS myelin, which contains several molecules that inhibit neurite outgrowth *in vitro*. In the opening session, Lisa Schnell (University of Zurich) detailed recent progress in understanding the myelin-based inhibitor Nogo-A, a highly conserved transmembrane protein that is normally present only in the CNS. Transgenic mice that express Nogo in PNS myelin led Dr Schnell to conclude that the effect of Nogo-A is to delay neuronal regrowth rather than inhibit it completely. This makes it likely that Nogo-A antibodies will need to be combined with additional treatments, an observation supported by the phenotype of knockout mice that lack various forms of Nogo (Binhai Zheng, Stanford University). Although some mutations are embryonic lethal, others are indistinguishable from wild-type mice. Identifying the reasons for this somewhat surprising observation is a challenge that will shed light on the full range of inhibitory influences that bear on neuronal regrowth in the CNS.

Genetic redundancy, in which alternative proteins 'take over' the function of deleted proteins, is often invoked to explain observations of this type. CNS myelin contains other neuronal growth inhibitors, such as MAG and OMgp, each of which interact with the same signalling protein (NgR) in neuronal membranes (Zhigang He, Harvard Medical School). Thus, rather than eliminating single inhibitory molecules, identifying small-molecule inhibitors of the NgR-signalling pathway could provide a way to neutralise simultaneously the effects of all three inhibitors.

It is clear that failure of axon regeneration in mature CNS is not just a consequence of myelin-associated inhibitors because, as the CNS matures, changes intrinsic to neurons themselves make them less able to extend neurites when cocultured with astrocytes. Comparing embryonic and mature neurons provides clues to the signalling molecules responsible for this difference (Derryck Shewan, Centre for Brain Repair, Cambridge). Pharmacologically manipulating key intracellular-signalling pathways by, for example, increasing cAMP and blocking Ca^{2+} release from intracellular stores increases outgrowth of neurites from mature axons *in vitro*.

The session on olfactory glia demonstrated that more information is needed before the full potential of these cells can be assessed. Jane Roskams (University of British Columbia) described the neuroprotective effects of olfactory glia in decreasing cavitation at the site of a crush injury, but highlighted that the unavoidable entry of Schwann cells to the lesion site might contribute to the responses attributed to olfactory glia. James Guest (Miami Project) described the issues involved with harvesting cells from the olfactory epithelium of primates. Populations of OECs collected from different areas also vary, depending on their source (Jane Roskams; Shaista Hayat, King's College, London), which opened a discussion about the relative merits of highly purified cells compared to more complex phenotypic mixtures.

Practical issues associated with the isolation and culture of human stem cells were reviewed by Maeve Caldwell (University of Cambridge). Since these have the potential to form neurons, oligodendrocytes and

astrocytes, determining how to prime stem cells in culture so that they create the desired phenotype is vital. David Becker (University College, London) also emphasised the complexities associated with developing novel therapies. Using antisense agents to reduce the synthesis of connexin 43, he demonstrated the importance of gap junctions in transmitting death signals from injured neurons to healthy neighbouring cells. Reducing transmission through gap junctions limits the spread of the injury, and possibly reduces glial scar formation and spares white matter.

Throughout the meeting, speakers returned to issues associated with growth factors. In work that is promising for those living with chronic SCI, Wolfram Tetzlaff (University of British Columbia) described how applying trophic factors to the cell bodies of very chronically injured neurons results in neural regeneration. Although applying neurotrophins increases neuronal sprouting and regrowth, it is clear that newly growing sprouts from dorsal root ganglion neurons need to be controlled, lest they develop aberrant connections that cause neuropathic pain (Matt Ramer, University of British Columbia). The possibility of developing autonomic dysreflexia is another potential problem, and work on developing a much needed model to determine the potential roles of distinct growth factors in either developing or alleviating this condition was described by Alexander Rabchevsky (University of Kentucky). Sasha brought the realities of human treatment home to the audience by describing his personal experience of this condition.

How best to administer growth factors was another of the issues covered. Ann Logan (University of Birmingham) described the issues involved in targeting synthetic vectors that encode growth factors to specific types of cells. The difficulties encountered make it difficult to envisage a universally applicable synthetic vector and alternative strategies may need to be considered.

Later in the day, Filitsa Groutsi (University College, London) detailed her progress with highly disabled herpes simplex virus vectors to deliver trophic factor genes and enhance regeneration.

An alternative strategy to deliver growth factors involves transplanting fibroblasts that have been engineered to secrete neurotrophins; and transplanting modified fibroblasts that secrete either BDNF or NT-3 improves behavioural outcomes and fibre outgrowth in acute lesions. Jacqueline Bresnahan (Ohio State University) described work undertaken as part of the ISRT Translational Network to investigate the effects of transplanting these fibroblasts in chronic contusion injuries in rats (in collaboration with the laboratories of Mark Tuszynski, Marion Murray and Itzhak Fischer). Although chronic thoracic contusion injuries (T9–10) gradually develop cavities similar to those of chronic human injuries, injection of growth-factor-secreting fibroblasts into these cavities has no apparent functional effects. Dr Bresnahan also described progress in developing chronic, cervical contusion injury model in rats. Unilateral contusion injury at C5–6 causes the animals to clench their forepaw and bend their elbow, resulting in deficits in the use of the forepaw in exploring a cylinder and grooming. Hind-limb deficits were only apparent when animals walked along a horizontal ladder. Characterisation of this new cervical contusion model provides an important resource for testing clinically relevant injuries in rats. A further model that is likely to be invaluable in preclinical studies of potential treatments was presented by Mark Tuszynski (University of California, San Diego), who is developing a primate model of SCI.

In a session devoted to human physiology, Nick Davey (Imperial College School of Medicine) gave an overview of the projects associated with the ISRT Clinical Initiative, which is developing the clinical measures needed to assess therapeutic outcomes in humans. Damage to motor pathways is being assessed using the muscle reflexes that result from mechanical stimulation of the spine and paraspinal muscles. Transcranial magnetic stimulation of the motor cortex combined with surface electrical recording from intercostal muscles is another promising measure of the completeness and level of upper thoracic injury, and might also induce plasticity; reducing inhibitory influences in the spinal cord could enhance motor function, as suggested by Xiang Yang Chen (State University of New York). Progress on clinical measures of the perceptual threshold to cutaneous thermal and vibratory stimulation in humans with chronic thoracic SCI was presented, as was progress with sensory and autonomic measures. This was a very brief snapshot of progress during the first full year of the Clinical Initiative, with the full range of studies to be discussed in more detail next year. On a related topic, Michael Craggs outlined initial studies to develop sensitive methods to measure changes in the supra-sacral sensory–motor pathways involved in bladder and bowel control.

In closing the meeting, Naomi Kleitman (National Institute for Neurological Diseases and Stroke, USA; NINDS) succinctly reviewed the previous 2 days and summarised the recent initiative announced by NINDS to advance translational and clinical research. In what could be seen as a tribute to the ISRT lead, this includes a range of measures intended to identify research strategies that are appropriate for translational studies, and the issues that remain to be addressed before starting clinical trials to test these in neurological diseases and injuries.

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