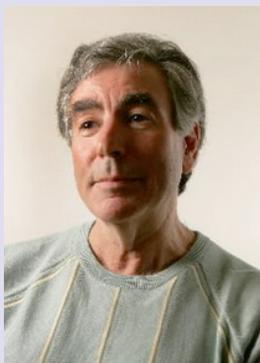


Neural Prosthesis Seminar

Functional Regeneration Beyond the Glial Scar

Friday, January 15, 2016 • 8:30 AM

Biomedical Research Building, Room 105
Case Western Reserve University



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Abstract

Over the past several decades, my lab has concentrated our research efforts learning about the molecules that reactive glia produce in the scar following spinal cord injury that actively block regeneration. Although highly controversial from its inception, my lab was one of the very first to suggest that an overtly growth inhibiting molecular environment might actually exist in the scar. One of the most interesting families of molecules, the lectican family of extracellular matrix associated sulfated proteoglycans and, in particular, the chondroitin sulfate proteoglycans, (CSPGs) were first discovered by my lab in the early 1990's to be critical in creating such regenerative glial boundaries.

To test the proteoglycan inhibition hypothesis in regenerative failure we pioneered the use of the CSPG degrading enzyme chondroitinase to reveal the important role of the glycosaminoglycan (GAG) sugar chains rather than the protein core in mediating axon growth inhibition. In 2009 and 2011, nearly 2 decades after CSPGs had first been implicated in regeneration failure, my lab was a major collaborator in the discovery of the first family of neuronal receptors for CSPGs that mediate the life long entrapment of cut nerve fibers within the scar. The lab has now generated small peptides, administered simply by sub-cutaneous injection, that block these receptors on damaged neurons in the lesioned spinal cord. Behavioral recovery particularly after acute administration of the peptide that blocks the sigma (σ) member of this so-called LAR receptor family was especially remarkable. Indeed, this novel, easily injectable, small peptide inhibitor allowed unprecedented levels of functional recovery following acute spinal cord injury, presenting a potential new avenue of treatment for paralysis especially in people with incomplete injuries. For those SCI patients with more complete injuries and those at chronic stages, an especially exciting development is our recent demonstration that combining the classical use of segments of autologous peripheral nerves as "bridges" to bypass a lesion of the adult rat spinal cord combined also with inhibitory matrix modification via chondroitinase plus the blocking peptides, allows regenerating axons to exit the bridge, form functional synapses, and restore useful movements to the once paralyzed limbs but more remarkably promotes robust functional recovery of the bladder. Our research strategy shows clearly, for the first time, that long distance regeneration, with appropriate re-formation of functional connections, can be achieved in the adult after catastrophic spinal cord injury even at chronic stages providing real hope that we are now entering an era where strategies for providing functional benefit in animal models of spinal cord injury are sufficiently robust that there should be optimism for translational success.

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