

**Stony Brook University  
The Graduate School**

Doctoral Defense Announcement

**Abstract**

The role of the tPA/plasmin proteolytic cascade after spinal cord injury

By

**Westley B. Nolin**

Paralysis resulting from spinal cord injury is devastating and persistent. One major reason for the inability of the body to heal this type of injury ensues from the local upregulation of chondroitin sulfate proteoglycans (CSPGs) at the site of injury, leading to the formation of the glial scar through which axons are unable to regenerate. Experimental approaches to overcome this physical and biochemical barrier have accordingly focused on reducing the inhibitory properties of CSPGs. For example, using chondroitinase to remove the sugar chains and reduce the CSPGs to their core protein constituents allows for some axonal regeneration through the glial scar, but does not provide dramatic functional recovery as a monotherapy.

In the current study we used *in-vitro* and *in-vivo* approaches to investigate a potentially synergistic therapeutic opportunity based on tissue plasminogen activator (tPA), an extracellular protease that converts plasminogen (plg) into the active protease plasmin. We show that tPA and plg both bind to the CSPG protein NG2, which functions as a scaffold to accelerate the tPA-driven conversion of plg to plasmin. The binding occurs via the tPA and plg kringle domains and is enhanced in some settings after chondroitinase-mediated removal of the NG2 proteoglycan side chains. Once generated, plasmin degrades NG2, both in an *in-vitro* setting using recombinant protein, and *in-vivo* in mouse models of spinal cord injury. Our finding that the tPA and plg binding is in some instances more efficient after exposure of the NG2 proteoglycan to chondroitinase treatment suggests that a combined therapeutic approach employing both chondroitinase and the tPA/plasmin proteolytic system could be of significant benefit in promoting axonal regeneration through glial scars after spinal cord injury.

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