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Neuraminidase for spinal cord injury

By Kai-Jye Lou, Staff Writer

Researchers at **The Johns Hopkins University School of Medicine** have shown that treatment with a recombinant bacterial neuraminidase can promote the recovery of motor and autonomic function in a rat model of spinal cord contusion injury.[1] The data suggest the enzyme, better known as a target of flu drugs, could provide a therapeutic option for spinal cord injury in humans.

The neuraminidase is easy to produce and stable at body temperatures for at least two weeks—factors that could make it an attractive development candidate. Neuraminidase is also called sialidase.

Following SCI, axon regeneration inhibitors such as myelin-associated glycoprotein (MAG) can accumulate at the site of injury and suppress neurite outgrowth. At least two companies are developing compounds that inhibit or clear such molecules from the injury site.

Novartis AG's ATI355, a mAb that inhibits reticulon 4 (RTN4; NOGO-A; NOGO), is in Phase I testing for SCI. Chondroitinase ABCI from **Acorda Therapeutics Inc.** is in preclinical development for the same indication and works by breaking down chondroitin sulfate proteoglycans (CSPGs).

Like MAG, CSPGs and NOGO are known to inhibit neurite growth.

Earlier studies by Johns Hopkins' Ronald Schnaar showed that bacterial neuraminidases cleave the MAG-binding terminal sialic acid residue from sialoglycans and increase axon outgrowth.[2–4] However, his team did not explore the functional consequences of neuraminidase-enhanced axon outgrowth.

"The rat peripheral nerve graft model we used in our previous study isn't designed for evaluating functional recovery," said Schnaar, a professor in the Department of Pharmacology and the Department of Neuroscience. "While it is a valid research model, it is not as relevant to human spinal cord injury as the rat contusion model we used in our current study."

Contusion injury models are good proxies for the human condition as they replicate the most common type of SCI.

In the new study in a rat model of contusion SCI, Schnaar's group showed that intrathecal delivery of a recombinant bacterial neuraminidase through an implanted catheter improved recovery of motor and autonomic function and increased axon sprouting compared with delivery of saline control ($p<0.05$ for all).

Results were published in the *Proceedings of the National Academy of Sciences*.

"The most exciting part of this study is that they applied this enzyme and detected beneficial effects in a spinal cord injury model that is relevant to patients," said Shuxin Li, assistant professor in the Department of Neurology at **The University of Texas Southwestern Medical Center at Dallas**.

In terms of druggability, Schnaar thinks that ease of production and stability could make the recombinant neuraminidase an attractive SCI therapeutic. The researchers achieved high-yield production of recombinant *Vibrio cholerae* neuraminidase by using an expression plasmid in *Escherichia coli*. Importantly, the neuraminidase retained about 90% of its activity after 12 days, which suggests the enzyme is stable *in vivo*.

"We've recovered it from implanted catheters and found that it retains nearly all its enzymatic activity even after two weeks," he told *SciBX*.

Regarding delivery, Schnaar thinks intrathecal administration is the preferred route. "We haven't yet tested the ability of neuraminidase to cross the blood brain barrier, but if we were to try delivering the enzyme outside the intrathecal space, my feeling is that we will dilute its efficacy," he said.

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>
> ***—Shuxin Li, The University of Texas Southwestern Medical Center at Dallas***

Combinatorial potential

Schnaar's group is now evaluating the use of recombinant neuraminidase plus a research-grade chondroitinase ABC vs. either compound alone in the rat contusion SCI model. He said his team also is considering combining the neuraminidase with anti-NOGO therapies. The chondroitinase is supplied by **Seikagaku Corp.**

Neither Acorda nor Novartis was available to comment on the *PNAS* paper.

Li thinks that targeting MAG binding on sialoglycans alone would have a limited effect and believes that targeting multiple growth-inhibiting molecules with a single compound is the way to go.

"MAG has been shown to suppress neurite outgrowth by binding to both NOGO receptors and sialoglycans," he told *SciBX*. "It is unlikely that partial blockade of MAG function alone will induce a large degree of axonal growth due to strong repression from other inhibitors as well as from NOGO receptor–mediated MAG suppression."

Indeed, Li wanted to know the molecular mechanisms responsible for the increased axonal growth and functional recovery attributed to neuraminidase. "The authors indicate that cleaving sialic acid residues from binding partners of MAG was the basis for improved axon sprouting and behavioral recovery, but they have not yet provided any molecular mechanisms" for these observed effects, he said.

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Li suggested that additional factors, such as the generation of the monosialoganglioside GM1, may have contributed to the improved recovery of the neuraminidase-treated rats in the *PNAS* paper. GM1, which has been suggested to have axon-promoting properties,[5,6] is the product of the reaction between neuraminidase and the trisialoganglioside GT1b, a MAG-binding sialoglycan.

Schnaar said his group has filed a patent application covering the use of neuraminidase to increase axon regeneration. He said the work is available for licensing through Johns Hopkins.

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COMPANIES AND INSTITUTIONS MENTIONED

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Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
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