An acid boost to SCI therapies

By Michael J. Haas, Senior Writer

In animals with spinal cord injury, the efficacy of stem cell transplants is limited by their tendency to differentiate into astrocytes instead of neurons. A team of Japanese researchers has overcome this obstacle by showing that valproic acid can both promote neuronal differentiation of neural stem cell transplants *in vivo* and help the recovery of motor function in mouse models of SCI.¹

Proinflammatory cytokines and other molecules upregulated at the site of an injured spinal cord cause neural stem cells (NSCs) to differentiate into astrocytes. This process helps form an astroglial scar that plays a protective role during healing, but the scars also secrete factors that limit the physical and functional recovery of damaged nerves.

Thus, a key challenge in developing NSC-based therapies to treat SCI has been directing transplants away from an astrocytic lineage and toward a neuronal one *in vivo*.

In 2004, researchers at the **Salk Institute for Biological Studies** and the **Nara Institute of Science and Technology** reported in the *Proceedings of the National Academy of Sciences* that the histone deacetylase (HDAC) inhibitor valproic acid induced neuronal differentiation and inhibited astrocytic and oligodendrocytic differentiation of murine NSCs *in vitro*.²

Generic valproic acid is approved to treat epileptic seizures, migraine and mania.

Based on those findings, a coauthor of the *PNAS* study, Kinichi Nakashima, assembled a team of Japanese researchers to investigate whether valproic acid would have the same effect on NSC transplants in mouse models of SCI.

The team found that mice with severe SCI receiving NSC transplants plus valproic acid recovered 50% of normal hind limb function compared with a 25% recovery rate in mice receiving only NSC transplants.

Immunohistological analysis showed that 20% of the surviving NSC transplants differentiated into neurons in the valproic acid-treated mice compared with less than 5% in the mice that did not receive the agent.

In vitro experiments confirmed that valproic acid's inhibition of HDAC was responsible for promoting the neuronal differentiation and neurite outgrowth of NSCs and also showed that transplant-derived neurons directly contributed to functional recovery in the treated mice.

Data were published in *The Journal of Clinical Investigation*.

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DaVinci Biosciences

Nakashima is a professor in the laboratory of molecular neuroscience at the Nara Institute's Graduate School of Biological Sciences. The team included scientists from **Kagoshima University** and **Osaka Prefecture University**.

Although using NSCs to treat SCI is not new, and stem cell transplants are often guided toward a particular differentiation fate *in vitro* before transplantation, the Japanese team's approach "is novel in that they are using valproic acid to guide the cells to a neuronal lineage *in vivo*," said Rafael Gonzalez, director of R&D at **DaVinci Biosciences LLC**.

Added Gonzalez: "The ideal therapy to treat SCI should be two-pronged, with cell transplants that result in a heterogeneous mix of cell types—but with more neurons and oligodendrocytes than astrocytes preferred—plus another component that supports the growth of endogenous tissue."

The Japanese team's approach appears to do just that by using valproic acid both to guide NSC transplants away from an astrocytic lineage and to support the outgrowth of endogenous neurons, according to Gonzalez.

DaVinci's DV-1, an autologous cell therapy made from bone marrow containing adult stem cells, is in a Phase I/II trial to treat SCI.

Going chronic

Gonzalez said the next step for Nakashima's team could be to test valproic acid plus NSC transplants in models of chronic SCI, which is

more representative of the SCI patient population than the acute SCI models used in the *JCI* paper.

"If they can show advantages of the combination therapy in models of chronic SCI, it would be fantastic," Gonzalez added.

Nakashima said his team would like to study the combination in models of chronic SCI but told *SciBX* "we cannot do this simultaneously with other projects because we have only a limited number of people in my lab."

Instead, the team first plans to test valproic acid in mouse models of SCI that receive transplants of human NSCs, human embryonic stem cells (hESCs) and induced pluripotent stem (iPS) cell-derived neural cells. "I thought that we'd better examine whether our method is also effective when we use human neural stem cells" before testing its therapeutic applications in other SCI models, Nakashima said.

Regardless of preclinical development, Gonzalez cautioned that clinical trials of the combination could be slow going. "There could be huge obstacles to developing a two-pronged approach because regulatory bodies will want to see the effect in humans of each agent separately before testing the combination," he said.

However, when a combination therapy includes a marketed product and a new therapeutic entity, 2006 guidance from the FDA, "Nonclinical Safety Evaluation of Drug or Biologic Combinations," indicates that preclinical safety studies on the new entity—first alone and then in combination with the marketed product—could be sufficient to support an IND filing for the combination.

Additionally, in June the FDA announced that it is soliciting comments on plans to develop guidance covering the co-development of two or more investigational drugs for use in combination, including combinations where one therapeutic increases the efficacy of the other without an independent therapeutic effect. Comments were due by Sept. 7.

The findings reported in *JCI* are neither patented nor partnered, Nakashima said.

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