Precursors upon MS

By Lev Osherovich, Senior Writer

Cleveland Clinic researchers have found a primitive type of cell in adult brains that can differentiate into myelin-generating oligodendrocytes.¹ The discovery could lead to new therapies for multiple sclerosis if researchers can figure out how to culture the cells or manipulate their growth and migration. **Vertex Pharmaceuticals Inc.** has nonexclusively licensed the technology, although the biotech is not disclosing specific plans for a potential foray into MS.

Oligodendrocytes are glial cells that wrap spindly projections around the axons of neurons, creating a myelin sheath that allows electrical conduction during neuronal activity. In MS, an autoimmune response against myelin proteins leads to destruction of the sheath and to neurological dysfunction.

Most MS therapies aim to curb the inflammatory autoimmune response that destroys myelin, but such approaches don't address the problem of how to restore damaged myelin. Bruce Trapp, professor of neurosciences at the Cleveland Clinic, thinks that problem could be solved by growing more oligodendrocytes.

In rats, Trapp previously found that oligodendrocytes express tubulin $\beta 4$ (TUBB4), a cytoskeletal protein involved in cell division and motility.²

In a new article in the *Journal of Neuroscience*, a team co-led by Trapp probed adult human brain slices with antibodies against TUBB4 and found a small population of TUBB4-positive cells within the subventricular zone. These cells lacked molecular markers typical of either glial cells or oligodendrocyte precursor cells.

The team then isolated Tubb4-expressing cells from rat brains, cultured the cells *in vitro* and found they spontaneously proliferated and differentiated into a full range of glial cells, including oligodendrocytes, astrocytes and neurons, depending on culture conditions.

Although it's unclear whether TUBB4 itself plays a role in the flexible nature of the cells, Trapp believes that TUBB4 is a marker for a distinct, primitive cell type that can develop into a variety of brain cells.

"These cells are not oligodendrocyte progenitor cells in the traditional sense, in that they don't express the markers of progenitors," said Trapp. "I think TUBB4 is identifying a new pre-progenitor cell."

The most immediate use of TUBB4 cells may be to grow new oligodendrocytes. In rats with a genetic defect in myelination that causes MS-like symptoms, implanted cultured TUBB4 cells differentiated into oligodendrocytes and regenerated the myelin sheaths of nearby neurons more effectively than conventional oligodendrocyte precursor cells.

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—Bruce Trapp, Cleveland Clinic

"In an acute demyelinating model, this cell type exceeds other cells," said Trapp. "You get more bang for your buck."

Therapeutic approaches

According to Trapp, the new cell type could be useful for regenerating myelin in one of two ways. First, TUBB4 cells could be cultured *in vitro* and transplanted into damaged brain regions. Second, endogenous populations of TUBB4 could be stimulated to divide and mobilize to damaged regions. Both approaches, however, face technical hurdles.

For autologous transplantation, TUBB4 cells would need to be isolated from an individual patient, expanded *in vitro* and then reintroduced into parts of the brain in which MS has caused neurodegeneration.

Another transplant approach could involve creating a human TUBB4 cell line that serves as a universal donor. The drawback is that such a cell line could trigger immunological responses against the graft.

Trapp is partial to the idea of cultivating TUBB4 cells for transplantation and thinks the cells could be especially useful for treating acute demyelination outside of the CNS such as that seen in transverse myelitis, an MS-like disease of spinal cord.

Although culturing Tubb4 cells from rat brains has been fairly straightforward, Trapp's team has not yet cultured human TUBB4 cells, in part because this would require biopsy of live human brains or fetal tissue. Experiments with fetal tissue are banned in Ohio.

"The challenge is to get enough of these cells from humans," said Trapp. "We're a little handicapped in Ohio because the best way to do this is to work with fetal tissue, which we can't do."

In any case, Robert Miller, professor of neurosciences and vice dean for research at **Case Western Reserve University School of Medicine** and a coauthor on the study, thinks isolating sufficient numbers of TUBB4 cells from humans is unlikely. "We're not going to solve the function deficits in MS by cell transplantation," he said.

Instead, Miller favors developing therapeutics that recruit endogenous TUBB4 cells to the sites of MS lesions.

Indeed, when the researchers examined brain samples from MS patients, they found TUBB4 cells in active MS lesion sites but not in adjacent nonlesion sites, suggesting the cells could migrate out of the subventricular zone in response to myelin damage.

However, even if TUBB4 cells are active at lesion sites, they may not do much good when myelin is under autoimmune assault. Miller thus noted that any cell-based regenerative strategy to treat MS must follow or accompany measures to control autoimmunity. "It will be necessary to control the initial inflammatory triggers of MS," he said.

To Miller, a better understanding of the signals used by TUBB4 cells to detect damaged myelin is the key to manipulating their behavior *in vivo*. "If you understand how they're regulated, you could encourage them to fill in the missing myelin," he said.

Robert Mays, senior director of regenerative medicine at **Athersys Inc.**, said either approach—transplanting TUBB4 cells or inducing them to migrate—will require extensive preclinical efforts.

“I would caution against predicting that this population of cells will have near-term utility in the treatment of MS,” he said. Mays cited the technical and ethical challenges of obtaining human TUBB4 cells for autologous or fetal transplant experiments.

He also noted that developing small molecule or growth factor therapies to influence the migration and differentiation of TUBB4 cells will require a lot of research, since it is not yet known what makes the cells grow and move.

Athersys is developing MultiStem, a biologic product consisting of multipotent adult progenitor cells (MAPCs), for a variety of indications. MultiStem cells are in Phase I trials both to treat acute myocardial infarction (AMI) and for bone marrow transplantation.

The company is collaborating with Miller to explore the use of MultiStem cells to treat MS. Mays said the cells could be useful for MS because they can be grown in large numbers *in vitro* from a patient’s bone marrow and have immunomodulatory properties that could reduce inflammation at lesion sites.

Miller’s research is supported by the **Myelin Repair Foundation** (MRF) a not-for-profit virtual biotech that is financing myelin regeneration research.

According to Trapp, Vertex has a nonexclusive license to the use of TUBB4 cells. Company spokesperson Jane Kramer said Vertex “does indeed have an interest in MS and regenerative medicine,” although the company declined to comment on the study.

The biotech company does have experience working with disease-related philanthropies. It has collaborated with **Cystic Fibrosis Foundation Therapeutics Inc.** to develop two compounds to treat CF: VX-770, a small molecule potentiator of CF transmembrane regulator (CFTR) that began Phase III trials in May, and VX-809, a small molecule CFTR corrector that entered Phase IIa studies in March.

Osherovich, L. *SciBX* 2(27); doi:10.1038/scibx.2009.1064
Published online July 16, 2009

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COMPANIES AND INSTITUTIONS MENTIONED

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