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REPRINT FROM JULY 28, 2011

Making myelin

By Lauren Martz, Staff Writer

Biogen Idec Inc. researchers have shown that knocking out tumor necrosis factor receptor superfamily member 21 in rodents provides two angles of attack in multiple sclerosis: decreasing inflammation and increasing remyelination.[1] The latter ability could lead to repair of damaged myelin and consequent blocking of disease progression, a key advantage over current MS drugs that mainly slow progression by lowering inflammation.

MS is an autoimmune disease characterized by destruction of the myelin sheath on axons that leads to a broad spectrum of neurological symptoms. Until recently, the disease was treated with immune-suppressing therapeutics, including Avonex interferon beta-1a from Biogen Idec, Rebif interferon beta-1a from **Pfizer Inc.** and **Merck KGaA** and Copaxone glatiramer acetate from **Teva Pharmaceutical Industries Ltd.** and **Sanofi**.

> **"These extensive, well-designed studies suggest that an anti-DR6 antibody has a direct effect on the survival and differentiation of DR6-positive immature oligodendrocytes and promotes remyelination independently of any anti-inflammatory activity."**
>
> *—Maurice Zauderer, Vaccinex Inc.*

These i.v. compounds were designed to dampen the immune system to slow progression, but about 30% of patients continue to progress.

Newer immune modulators on the market include Rituxan rituximab from Biogen Idec, **Roche** and Roche's **Genentech Inc.** unit, Tysabri natalizumab from **Elan Corp. plc** and Biogen Idec and Gilenya fingolimod from **Novartis AG** and **Mitsubishi Tanabe Pharma Corp.**

These drugs have shown strong data in slowing disease progression and preventing further tissue damage, but mechanistically they still target the inflammation that causes neurological damage and do not resolve the damage itself.

Sha Mi and colleagues at Biogen Idec set out to see if they could repair the neurons damaged in MS by increasing the remyelination properties of axons. The result was the discovery of a new target—tumor necrosis factor receptor superfamily member 21 (TNFRSF21; DR6)—that might be preventing remyelination.

Mi is lead author and principal investigator in neurobiology at the company. The team included a researcher from the **Case Western Reserve University School of Medicine**.

Previous work has shown that DR6 is broadly expressed on developing neurons and is required for normal neuronal cell death. Aberrant activation has been associated with neuronal degeneration in Alzheimer's disease (AD).[2]

Mi's team showed that in mouse oligodendrocyte progenitor cells (OPCs), small interfering RNA against Dr6 decreased caspase-3 (Casp3; Cpp32) activation and cell death compared with control siRNA. Both the survival and differentiation of OPCs are required for myelination of CNS axons.

Cultured OPCs from *Dr6*$^{-/-}$ mice had greater maturation and survival than cells from wild-type mice.

In rats already exhibiting symptoms of experimental autoimmune encephalomyelitis (EAE), intraperitoneal injection of an anti-Dr6 decreased disease severity and increased the number of remyelinated axons in EAE lesions compared with injection of a control antibody. The treatment also decreased infiltration of T cells into the spinal column, suggesting that in addition to remyelinating axons, DR6 antagonism also might decrease inflammation.

Finally, the researchers showed that DR6 levels were higher in brain slices from MS patients than in slices from healthy brains.

The findings were published in *Nature Medicine*.

"These extensive, well-designed studies suggest that an anti-DR6 antibody has a direct effect on the survival and differentiation of DR6-positive immature oligodendrocytes and promotes remyelination independently of any anti-inflammatory activity," said Maurice Zauderer, president and CEO of **Vaccinex Inc.**

He noted that the team saw the effect in rat models of both inflammation and non-inflammation–associated demyelination. "It is important to distinguish between attenuated demyelination that may result from inhibiting destructive inflammation and the actual repair and reversal of damage to CNS tissue," he added.

Vaccinex's VX15/2503, an anti–semaphorin 4D (SEMA4D) antibody, is in Phase I testing to treat cancer and is expected to enter the clinic for MS in early 2012. SEMA4D increases activation of immune and inflammatory cells while also promoting apoptosis and inhibiting differentiation of OPCs.

Researchers interviewed by *SciBX* wanted proof that systemic delivery of a DR6 antagonist would result in sufficient levels of the compound in the brain without being toxic to non-CNS tissues.

According to Zauderer, "DR6 is expressed on a large number of other tissues in addition to the brain including the thymus, lymph nodes, heart, pancreas, kidney, lung and colon. The effects of antago-

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OFFICES

BioCentury Publications, Inc.
San Francisco
PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333

Chadds Ford
223 Wilmington-West Chester Pike
Chadds Ford, PA 19317
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Tokyo
Chiyoda Building 6F
2-37 Ichigayatamachi
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T: +81 3 3267 8751

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nizing DR6 on these tissues are unknown."

Tassie Collins, director of translational medicine at the **Myelin Repair Foundation**, added that "DR6 is part of the TNF receptor superfamily with about 30 members, so they will need to make sure that their antagonist has good selectivity for DR6 and to make sure that there is no safety issue with off-target effects."

Mi responded that there was no evidence of toxicity or off-target effects in the knockout mice. "The DR6 knockout animals show a normal phenotype" with no abnormal behaviors, she said.

Remyelination

Biogen Idec is identifying a lead DR6 antibody to treat diseases involving demyelination such as MS. A DR6 inhibitor would be the company's second therapeutic aimed at remyelination.

The company's BIIB033, an antibody against leucine-rich repeat neuronal protein 1 (LINGO-1), is in Phase I testing to treat MS. LINGO-1 is a negative regulator of OPC differentiation and axon myelination.

Inhibitors of both DR6 and LINGO-1 should be well suited to treat secondary progressive MS, a form of the disease that involves accumulation of demyelinated neurons. Patients with the earlier form of relapsing-remitting MS could also benefit from blocking DR6, but the acute attacks during that disease stage are already controllable with immunomodulatory therapeutics.

"In general, anti-inflammatory drugs do not offer comparable benefits in patients in later-stage secondary progressive disease, which is characterized by continuing demyelination and axonal loss even in the absence of overt inflammation," said Zauderer.

"The available drugs are successful at targeting the initial part of the disease, but now we need to find a way to target the damage that has already been caused in order to start healing," added Collins. "The Myelin Repair Foundation is enthusiastic about Biogen's research into targets for myelin repair."

Biogen Idec has filed a patent application covering DR6 antagonism, and the IP is unavailable for licensing.

Martz, L. *SciBX* 4(29); doi:10.1038/scibx.2011.812
Published online July 28, 2011

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   Contact: Sha Mi, Biogen Idec Inc., Cambridge, Mass.
   e-mail: sha.mi@biogenidec.com
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COMPANIES AND INSTITUTIONS MENTIONED

Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
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