EMMPRIN's new clothes

By Steve Edelson, Executive Editor

EMMPRIN dropped off the drug discovery map in 2003 when Abgenix Inc.'s antibody against the target failed in a Phase II/III trial to treat graft-versus-host disease. Now, findings from Canadian researchers suggest it might be worthwhile to revisit this extracellular matrix metalloproteinase inducer in multiple sclerosis.¹ The researchers have antibodies against the target and are seeking an industry collaborator.

EMMPRIN (basigin Ok blood group; BSG; CD147) is a master regulator of matrix metalloproteinases (MMPs) and plays a role in leukocyte activation. Prior research has implicated a number of MMPs in MS, including MMP12, which is the target of **Vernalis plc's** small molecule V85546.

Despite the established link between MS and MMPs, Voon Wee Yong, professor in the Departments of Clinical Neurosciences and Oncology at the University of Calgary, noted that there is no literature on EMMPRIN specifically in the context of MS. "Knowing that downstream effectors of EMMPRIN are upregulated in the disease, it seemed quite reasonable for us to engage in further investigations," he told *SciBX*.

In a mouse model of experimental autoimmune encephalomyelitis (EAE), Yong's team observed upregulation of *Emmprin* on peripheral leukocytes before the signs of disease appeared.

In the diseased animals, *Emmprin* also was upregulated in leukocytes that infiltrated the CNS and in other cell types that reside in the brain.

The researchers also saw high *EMMPRIN* expression in brain samples from MS patients compared with in brain samples from healthy controls. Expression was highest in the plaque-containing areas of the brain samples.

"All of these data points are correlations," Yong noted, and as a result it wasn't yet clear whether EMMPRIN was correlated with disease or actually causative. "We wanted to know what happens if you perturb EMMPRIN."

Indeed, a research reagent anti-*Emmprin* antibody decreased disease severity in EAE mice compared with a control antibody. The reduction was accompanied by less infiltration of leukocytes into the CNS.

Data were published in *The Journal of Neuroscience*.

Timing is everything

The antibody studies did more than point to a causal role for EMMPRIN in MS—the findings also painted a mechanistic picture of when and how the target elicits its effects.

In particular, the anti-EMMPRIN antibody had no effect when it was given during the eight days after induction of EAE, a time during which leukocytes become activated. Thus, although EMMPRIN plays a role in leukocyte activation, Yong's group was able to rule out that mechanism in treating the disease.

Mice receiving the antibody during days 8–11 after disease induction told a different story, as those animals improved dramatically. During that four-day window, leukocytes migrate into the CNS.

Thus, said Yong, "the process is that leukocytes are activated in the periphery but don't penetrate into the CNS parenchyma until they make MMPs that help them break down the glia limitans," the final barrier before the CNS parenchyma.

"Blocking EMMPRIN is particularly useful during leukocyte migration," said Yong, who was corresponding author on the paper.

However, Yong does not expect the narrow dosing window to limit the use of anti-EMMPRIN antibodies.

"I'd see this as treatment for the relapsing-remitting form of the disease, where the relapse represents leukocytes getting activated," he said. An EMMPRIN inhibitor could help ward off the relapses in this patient population, he said, in two ways. The antibodies could prevent the activation of leukocytes and stop the CNS infiltration of any leukocytes that do become activated.

In addition, Yong thinks an anti-EMMPRIN antibody could have a good safety profile.

"EMMPRIN is normally expressed at basal levels and only gets upregulated in the context of an inflammatory insult," he said. "Our approach is to inhibit only the aberrantly upregulated EMMPRIN, which we think should give a safety margin. In that regard it's different from treatments that deplete immune cells—even those that are not activated."

Yong's team has generated its own antibodies against EMMPRIN. The specificity of the research tool antibodies "wasn't completely defined and it wasn't clear whether we would have the activity we seek," he said. "We made our own by targeting a site on the EMMPRIN molecule that we think is quite important in upregulating MMPs."

The University of Calgary has filed for a patent covering the antibodies, and the IP is available for licensing. Chris Nicholls, a technology analyst in the university's technology transfer arm, said the institution is "fielding inquiries from a number of pharmaceutical companies and other organizations with regard to its commercialization."

Edelson, S. *SciBX* 4(7); doi:10.1038/scibx.2011.183
Published online Feb. 17, 2011

REFERNECES

1. Agrawal, S.M. *et al. J. Neurosci.*; published online Jan. 12, 2011; doi:10.1523/JNEUROSCI.3659-10.2011
Contact: V. Wee Yong, University of Calgary, Calgary, Alberta, Canada
e-mail: vyong@ucalgary.ca

COMPANIES AND INSTITUTIONS MENTIONED

University of Calgary, Calgary, Alberta, Canada
Vernalis plc (LSE:VER), Winnersh, U.K.