New avenues in MS

By Lauren Martz, Staff Writer

Teams at the **Karolinska Institute** and **The University of Tokyo** have separately disclosed new targets for multiple sclerosis. Intervention in their pathways could yield new MS therapeutics if the pathways can be targeted more specifically than the standard therapies of steroids and interferon- β .

MS is an autoimmune disease that causes neurological inflammation and demyelination. Recent studies have shown that dysfunctional T helper type 1 (TH1) and TH17 cells cause autoreactivity, which can prompt the immune system to attack the myelin sheath around neurons.¹ Thus, many groups are focused on identifying the pathways that lead to the aberrant T cell activation.

In a paper published in *Science Translational Medicine*, a Karolinska team reported that increased levels of Vav 1 guanine nucleotide exchange factor (VAV1), a protein involved in T and B cell activation, are associated with MS.²

Meanwhile, the University of Tokyo researchers identified microsomal prostaglandin E synthase-1 (PTGES; mPGES-1) as a target involved in the development of pathogenic T cells. That study was published in the *Proceedings of the National Academy of Sciences*.³

"There are existing therapies that do work to some extent, but in MS, there is still an unarguable unmet medical need. We need safer, better treatments. These studies could represent new ways of moving towards those treatments," said Hideki Garren, EVP, COO, CSO and cofounder of autoimmune company **Bayhill Therapeutics Inc.**

Homing in on VAV1

The Karolinska team previously showed that a region on rat chromosome 9 played a role in the development of experimental autoimmune encephalomyelitis (EAE), a rodent model of MS. Now, Tomas Olsson, professor of neurology at the institute, and colleagues have shown that *Vav1* houses the locus.

In rats, *Vav1* mutations were more strongly associated with EAE than wild-type *Vav1*.

To translate the animal results into human disease, the team conducted a case-control study comprised of 7 independent cohorts and a total of 12,735 individuals. The study showed that the rs2546133-rs2617822 haplotypes in the first intron of *VAV1* were strongly associated with the disease. Both haplotypes led to increases in *VAV1* mRNA expression.

VAV1 mRNA also was increased in mononuclear cells from MS patients, and the increase correlated with higher levels of inflammatory cytokines such as tumor necrosis factor (TNF) and interferon- γ (IFNG; IFN- γ) in peripheral blood and cerebrospinal fluid.

Taken together, the results suggest that upregulation of *VAV1* is linked to the inflammatory autoimmune component of the disease and that decreasing levels of the protein or the mRNA could help treat MS.

"It would be of interest to explore, by high throughput screening, low molecular weight drugs that might dampen *VAV1* activity," said Olsson.

Olsson did say that additional studies will need to look at the biology of *VAV1* variants and their role in regulating the disease.

Brian Lawson, assistant professor of immunology and microbial sciences at **The Scripps Research Institute**, agreed. "They identified a substitution that increased its mRNA. However, this doesn't answer whether *VAV1* needs to be activated" via phosphorylation for the disease to occur, he said. "At this point, it is unclear what exactly the increased levels of *VAV1* do to relate to the disease if it is not activated.

What they need to show is that it is actually increased phosphorylated *VAV1* that is linked to the disease."

Ari Green, assistant of neurology and assistant director of the **University of California, San Francisco** MS Center, told *SciBX* it also would be good to determine whether blocking *VAV1* has deleterious effects before considering it as a potential therapeutic target. He pointed out that *VAV1* knockout suggests decreased numbers of profoundly dysfunctional lymphocytes. "Clearly the protective *VAV1* haplotype only has a partial effect on the protein's function," he said.

Olsson said his team's findings are not patented and that his group is open to collaborations and licensing with the pharmaceutical industry.

Watching mPEGS-1

While the Karolinska team focused on the inner workings of rat chromosome 9 to identify causative mutations in MS, Satoshi Ishii and colleagues at the University of Tokyo focused on the arachidonic acid (AA) signaling cascade.

The AA metabolic pathway produces eicosanoids involved in the immune response. Previous studies have shown that inhibiting cytosolic phospholipase A₂ (PLA₂) or cyclooxygenase (COX) in the pathway is effective at blocking MS but causes gastrointestinal ulcers and cardiovascular events.^{4,5}

PLA₂ functions far upstream in the pathway to mediate the release of AA from membrane glycerophospholipids. Further downstream, AA is converted into eicosanoids such as COX.

To further complicate the matter, there are more than 20 different eicosanoids downstream of PLA₂, and the effects of AA are pleiotropic. Thus, Ishii's team delved deeper into the pathway and used AA cascade-targeted lipidomics to identify the precise elements involved in MS.

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The University of Tokyo**

An analysis of the spinal cords, spleens and plasma of mice with EAE, as compared to those of healthy mice, showed that mPGES-1 levels were higher than those for other downstream elements in the EAE mice.

In the mice, disruption of *mPGES-1* completely blocked the production of prostaglandin E₂ (PGE₂), an eicosanoid that is synthesized by mPGES and whose levels are increased in MS. The knockout mice had less severe disease and their lymph nodes had lower TH1 and TH17 production in EAE lesions than healthy mice.

The researchers also found that *mPGES-1* was overexpressed in brain tissue samples from MS patients.

Ishii, an associate professor in the Department of Biochemistry and Molecular Biology at the University of Tokyo, said the “development of inhibitors of mPGES-1 is essential because no specific inhibitors are currently available for clinical and even experimental usage.”

UCSF’s Green said specificity would need to be the focus when developing inhibitors of a prostaglandin-related enzyme such as mPGES-1. Prostaglandin has widespread biological effects in many areas, he noted. “It will be important to replicate the desired effect of blocking mPGES-1 using a candidate molecule without affecting other products of AA metabolism.”

Ishii told *SciBX* that the findings have neither been patented nor licensed.

Getting to the specifics

Although both *mPGES-1* and *VAV1* appear to play a role in the genetic cause of MS, some researchers think inhibiting the targets may have effects that are too broad.

For example, Lawson said an inhibitor of VAV1 phosphorylation “would be a general immune suppressor and therefore could have the same problems that exist with current MS therapeutics” such as steroids and interferon- β (IFN β).

“The same applies to the lipid paper,” he added. “While they knock out a downstream enzyme of COX-2 and get a nice result, this pathway is upregulated in many inflammatory and autoimmune diseases. Intervening with the pathway takes you back to a general immune suppressant. A novel therapy would target the autoantigen-responding T cells while leaving the polyclonal T cell pool, the rest of the T cells, mostly unaffected, thus not resulting in general immune suppression.”

Bayhill’s Garren also noted that the new targets “are not antigen

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specific.” As a result, he said, “they may not achieve the balance of safety and efficacy that will be required to enter the market.”

Olsson disagreed. “Interference with the VAV1 pathway for sure intervenes with the mechanisms operative in MS—it may therefore be more disease specific” than general immunosuppressants, he said.

Likewise, Ishii thinks that inhibiting mPGES-1 could yield a therapy that addresses underlying MS etiology.

Regardless of specificity, Garren thinks that compounds against the new targets would likely

be used in combination with existing treatments. “The field as a whole is headed in that direction—combination therapies are already being clinically tested and might boost efficacy,” he said.

Bayhill’s antigen-specific DNA vaccine, BHT-3009, has completed a Phase IIB trial to treat MS. The plasmid encoding human myelin basic protein (MBP) did not meet the primary endpoint of significantly reducing the mean rate of new gadolinium-enhancing lesions compared with placebo. According to Garren, the company is “evaluating multiple options that will move the compound further in clinical development, including a potential partnership.”

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Contact: Tomas Olsson, Karolinska Institute, Stockholm, Sweden
e-mail: tomas.olsson@ki.se
Contact: Abdelhadi Saoudi, Institut National de la Santé et de la Recherche Médicale (INSERM), Toulouse, France
e-mail: abdelhadi.saoudi@inserm.fr
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Contact: Takao Shimizu, The University of Tokyo, Tokyo, Japan
e-mail: tshimizu@m.u-tokyo.ac.jp
Contact: Satoshi Ishii, same affiliation as above
e-mail: mame@m.u-tokyo.ac.jp
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COMPANIES AND INSTITUTIONS MENTIONED

Bayhill Therapeutics Inc., San Mateo, Calif.
Karolinska Institute, Stockholm, Sweden
The Scripps Research Institute, La Jolla, Calif.
University of California, San Francisco, Calif.
The University of Tokyo, Tokyo, Japan