Predictive biomarkers for MS

By Lauren Martz, Staff Writer

Stanford University and **Pfizer Inc.** researchers have reported that levels of IL-7 could help predict which multiple sclerosis patients will not respond to interferon- β therapy.¹ Serum analysis of IL-7 together with a second marker identified last year by the Stanford team, IL-17F, which was only able to identify about 10% of nonresponders on its own, could predict up to one-third of nonresponders.

Stanford has spun out **Atreca Inc.** to develop predictive blood tests based on the findings.

Interferon- β (IFN β ; IFN- β) is the standard first-line treatment for patients with relapsing-remitting multiple sclerosis (RRMS). Up to 25% of patients do not respond to the drugs, and treatment can even exacerbate the disease in some cases.

"The ability to identify patients who will versus patients who will not benefit from interferon- β is going to make an impact on aspects of MS management," said John Lin, executive director of experimental medicine at Pfizer's **Rinat Neuroscience Corp.** "Those patients who will not likely respond can move quickly on to alternative therapies without the worsening of the ongoing disease or the side effects."

Alternative therapies include Copaxone glatiramer acetate, a selective MHC II modulator marketed in the U.S. by **Teva Pharmaceutical Industries Ltd.** and in Europe by Teva and **Sanofi**; Tysabri natalizumab, an antibody that targets integrin β_4 (VLA-4; CD49D) from **Elan Corp. plc** and **Biogen Idec Inc.**; and Gilenya fingolimod, a sphingosine 1-phosphate receptor agonist from **Novartis AG**.

In 2010, a Stanford team including researchers from the current team found that patients with a form of MS driven by the T helper type 1 (Th1) subset of T cells have low levels of IL-17F and are generally responsive to IFN- β therapy, whereas patients with a form of MS driven by Th17 cells are more likely to relapse.²

Now, Lin, Lawrence Steinman and colleagues have found that high serum levels of IL-7 could indicate an increased chance of response to first-line therapy, particularly in patients who also have low levels of IL-17F. Steinman is professor of neurology and neurological sciences and pediatrics at Stanford University's Beckman Center for Molecular Medicine.

In a retrospective analysis of data from 26 RRMS patients treated

with IFN- β , those with high serum IL-7 levels responded to treatment and remained relapse free for 2 years after treatment. Patients with lower levels were less likely to respond. The serum analysis also showed that IL-7 levels inversely correlated with IL-17F levels, and patients with both low IL-17F and high IL-7 were most likely to respond to treatment.

In cultured, naïve human T cells, IL-7 induced differentiation into the Th1 cell phenotype but did not promote differentiation or proliferation of Th17 cells. This suggests IL-7 induces the Th1 cell-driven subset of MS cases.

In a mouse model of experimental autoimmune encephalomyelitis (EAE), an antibody against IL-7 receptor (IL-7R; CD127) lowered disease severity and peripheral T cell accumulation compared with control.

These findings suggest that in addition to being a biomarker, IL-7 might be a drug target because it directly contributes to disease pathology. Previous genetic studies identified a mutation in the *IL-7R* gene that was associated with MS susceptibility and showed that MS patients had higher levels of IL-7R and its IL-7 ligand than patients with noninflammatory neurological diseases,³ but the specific role of the cytokine in the disease remained unclear.

The new results were published in *Science Translational Medicine*. The paper also included researchers from **Walker Bioscience**, the

Radboud University Nijmegen Medical Centre and the **VU University Medical Center**.

Steinman told *SciBX* that "the combination of markers, IL-7 and IL-17F taken together, should be more useful than a single marker. Large-scale studies indicate that with one marker, IL-17F, we may be able to identify a group of nonresponders with very high specificity, approaching 100%. This will only cover about 10% of the nonresponders, however. The combination should be more informative."

Steinman told *SciBX* that patients with high levels of IL-17F and low levels of IL-7 represent up to 34% of nonresponders.

Predictive markers

Steinman told *SciBX* that three large-scale validation studies are under way looking at serum levels of IL-17F and IL-7 as biomarkers for responsiveness to IFN- β .

He said the retrospective trials are being run by **Bayer AG**, the EU and the **Karolinska Institute**, and they include more than 526 patients in total.

Steinman said Stanford has filed for a patent covering the biomarkers and has granted Atreca an option to develop diagnostics and therapeutics based on the biomarkers.

Richard Ransohoff said that validation studies will be key because the Stanford study included only a small number of patients and followed those patients for only two years. He also noted that relapses might not be the best way to identify nonresponders.

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Rinat Neuroscience Corp.**

“For relapsing-remitting MS patients, the goal is not necessarily to prevent relapses with therapeutics, unless they are particularly debilitating, but it is to prevent patients from advancing to the progressive phase of disease,” he said.

Ransohoff said that in long-term follow-up studies after clinical trials, relapses during the first two years of treatment indicated a possibility that the patient's disease would progress, but this risk of progression was equally seen in placebo patients as well as those on interferon. “A more accurate indication that a patient is not responding to interferon is the appearance of new MS lesions on MRI scans. New or enlarging lesions suggest that a patient's disease is at risk of progressing, and this predictive indicator was more specific to patients receiving interferon,” said Ransohoff.

Steinman said that the validation studies will also use relapse as the method to define nonresponders.

Ransohoff is director of the Neuroinflammation Research Center, staff neurologist at the Mellen Center for MS Treatment and Research and professor of molecular medicine at the **Cleveland Clinic Lerner College of Medicine of Case Western Reserve University**. He also advises **GlaxoSmithKline plc**, which has an IL-7R program, and has advised Bayer's Bayer Healthcare unit and Biogen Idec on biomarkers of interferon response in MS patients.

Lin told *SciBX* that Pfizer has filed a patent application for the IL-7 antibody work and that the IP is unavailable for licensing. Pfizer did not disclose whether they are pursuing clinical development of an anti-IL-7 antibody.

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COMPANIES AND INSTITUTIONS MENTIONED

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Bayer AG (Xetra:BAY), Leverkusen, Germany
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