New role for Actos in MS

By Lev Osherovich, Senior Writer

Industry has targeted peroxisome proliferation–activated receptors for metabolic indications since the 1990s. Now, a paper by German researchers suggests the PPAR agonist Actos pioglitazone could be useful for treating multiple sclerosis and other autoimmune diseases.[1]

The study assessed the effect of pioglitazone on experimental autoimmune encephalomyelitis (EAE), a widely used mouse model for MS. The drug appears to block the development of T helper type 17 (Th17) cells, which are implicated in autoimmunity.[2]

"There have been many publications about what determines the differentiation of Th17 cells," said Percy Knolle, professor of molecular medicine at the **University of Bonn** and senior author of *The Journal of Experimental Medicine* paper describing the pioglitazone findings.

Because Th17 cells are the prime suspects in amplifying the severity of autoimmune diseases, the pioglitazone finding "extends beyond MS," said Knolle, and "could have relevance for rheumatoid arthritis or other autoimmune diseases."

Actos activates peroxisome proliferation–activated receptor-γ (PPARG; PPARγ) and is marketed by **Takeda Pharmaceutical Co. Ltd.** and **Eli Lilly and Co.** to treat type 2 diabetes, macrovascular disease and dyslipidemia.

> **"PPARs have considerable potential as targets for immunomodulatory therapy."**
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> *—Christopher Glass, University of California, San Diego*

PPAR agonist in action

Based on earlier work,[3] Knolle's team suspected that activating PPARγ could reduce the intensity of the immune response to self-antigens. The team found that mice treated with pioglitazone and then injected with a brain-specific autoantigen had less severe EAE pathology than untreated controls. Conversely, PPARγ knockout mice developed more severe EAE than wild-type controls.

The team uncovered the Th17 cell connection by monitoring cytokine levels in mice treated with pioglitazone. Drug-treated mice had lower overall Th17 cell counts and lower levels of IL-17, the hallmark proinflammatory cytokine produced by Th17 cells, than untreated controls.

Knolle suspects that pioglitazone blocks the development of Th17 cells from naïve $CD4^+$ precursor cells. Indeed, pioglitazone blocked the production of the τ isoform of RAR-related orphan receptor C (RORC; RORγ), a transcription factor needed for Th17 cell differentiation.

Because PPARγ agonists reduce cellular lipid levels, Knolle suspects that pioglitazone's effect on RORγ and Th17 cell differentiation may be due to changes in lipid metabolism in naïve T cells.

"There are a number of endogenous mediators that control Th17 development," said Knolle. "These mediators, which may be intrinsic lipids, direct cells to differentiate into Th17 cells to promote autoimmunity."

Knolle's next step is to identify and block the production or activity of the Th17 cell–inducing lipids that he suspects provide the mechanistic link between PPARγ and RORγ.

Ajay Chawla, assistant professor of medicine at **Stanford University**, said Knolle's findings are consistent with earlier studies of PPARγ agonists in autoimmune disease models. The main advance in Knolle's study, said Chawla, is the identification of the specific cellular and molecular mechanisms affected by PPARγ agonists.

"They're able to nail it down to a cell-intrinsic effect on RORγ," he said.

In addition, Chawla said his own team has recently discovered a role for peroxisome proliferation–activated receptor-δ (PPARD; PPARδ) in autoimmunity. A report on these findings is in the press in a peer-reviewed journal, he said.

ROR of the crowd

Knolle thinks PPARγ agonists could be a relatively safe addition to the armamentarium of MS therapeutics, but cautioned that pioglitazone may not be suitable because of off-target metabolic and cardiovascular effects.[4]

Knolle noted that PPARγ agonists modulate autoimmunity and that people who are treated with these drugs are not immunosuppressed like patients receiving glucocorticoids and certain MS biologics.

"PPARs have considerable potential as targets for immunomodulatory therapy," said Christopher Glass, professor of cellular and molecular medicine at the **University of California, San Diego** and a coauthor of the paper.

Glass noted that rather than using broad-acting PPARγ agonists to treat autoimmunity, companies would likely want to tailor the site of action and PPAR subtype specificity to maximize the suppression of autoimmunity while minimizing cardiovascular and metabolic effects.

"The challenge will be for pharmaceutical companies to develop ligands that are optimized for regulating immunomodulatory activities as opposed to activities that are associated with unwanted side effects," said Glass.

According to Chawla, pioglitazone is a good candidate for an MS therapeutic. He said the drug should probably be positioned for use in patients who do not already have high Th17 cell levels.

"The question is whether, if you already have the disease, the drug will be sufficient to suppress the number of Th17 cells," Chawla said.

Knolle acknowledged that mice that had already developed EAE did not benefit from pioglitazone. Instead, Knolle thinks the drug might

potentially be useful to prevent flare-ups of relapsing-remitting MS, a form of the disease characterized by periodic episodes of brain infiltration by Th17 cells.

Over 20 companies have PPAR agonists in development for metabolic disorders. The other PPAR agonist on the market is **GlaxoSmithKline plc**'s Avandia rosiglitazone, which is approved to treat type 2 diabetes.

Takeda and GlaxoSmithKline declined to comment on Knolle's study.

One company keeping a close eye on the role of PPAR in autoimmunity is **Dara BioSciences Inc.** The company is developing next-generation PPAR agonists, and its lead compound is DB959, a dual PPARγ/PPARδ agonist that is in Phase I testing for type 2 diabetes and dyslipidemia.

"The understanding of how PPAR agonists can modulate inflammatory processes is certainly evolving rapidly," said Mary Kay Delmedico, project leader of Dara's PPAR program.

The next steps, said Delmedico, are to understand how tinkering with the relative activity of different PPARs could affect autoimmunity.

"Is a full PPARγ agonist the best choice or is a partial γ agonist or a dual γ/δ agonist better?" Delmedico asked. "Should one progress a currently marketed PPAR agonist, or could better results be obtained in these *in vitro* and *in vivo* models using a novel agonist?"

Knolle has filed for a patent covering his team's discoveries and said the IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

Dara BioSciences Inc. (NASDAQ:DARA), Raleigh, N.C.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
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