Taming T cells in T1D

By Lev Osherovich, Senior Writer

Separate teams at the **University of California, San Francisco** and **Pfizer Inc.** have evidence that blocking IL-7 signaling in mice can arrest the autoimmune activity behind type 1 diabetes.^{1,2} Whether the findings will translate to the clinic depends on whether the cytokine has the same effects on helper T cell activity in mice and humans.

IL-7 is a key regulator of helper T cells, which ordinarily orchestrate the immune response to foreign antigens. In 2007, researchers at the **Karolinska Institute** found evidence that IL-7 also plays a role in autoimmune disease. The group uncovered human genetic variants in *IL-7 receptor (IL-7R; CD127)* that increased the risk of multiple sclerosis (MS) compared with wild-type IL-7R.³

Also in 2007, researchers at the **University of Cambridge** linked these variants to type 1 diabetes (T1D).⁴

"A lot is known about IL-7 in maintaining T cell homeostasis," said John Lin, leader of the Pfizer team and VP of experimental medicine at Pfizer's **Rinat Neuroscience Corp.** unit. "When lymphocyte numbers are really low, IL-7 can restore T cell levels. Its genetic association with autoimmune disease led people to start to look at alterations in IL-7 signaling" as a potential therapeutic target.

Indeed, the Pfizer team reported last year that an antibody against IL-7r reduced disease severity in a mouse model of MS.⁵

"The idea is that if you block IL-7 you'll block the development and survival of T cells" that are causing an aberrant response to self antigens in autoimmune disease, said UCSF team leader Hans Doms, who has since become an assistant professor of medicine at the **Boston University School of Medicine**.

Repressed memory

The Pfizer and UCSF teams pursued a similar approach in diabetes. In a nonobese diabetic (NOD) mouse model, animals were infused weekly with anti-IL-7r mAbs or a nonspecific antibody and monitored for signs of autoimmunity. Whereas mice given the control mAb spontaneously developed type 1 disease, mice receiving the anti-IL-7r mAbs remained healthy.

The anti-IL-7r antibodies decreased levels of proinflammatory cytokines linked to type 1 diabetes progression compared with control antibody.

Mice on anti-IL-7r immunotherapy also had higher insulin secretion and lower levels of T cell activity in lymph nodes and pancreatic islets.

In mice already beginning to lose β cell mass to autoimmune attack, the anti-IL-7r therapy led to better glycemic control in about 50% of these mice compared with control antibody.

Histopathological analysis of mice with the disease revealed immune cells were present—but quiescent—in pancreatic islets. This suggested that anti-IL-7R treatment caused a shutdown of immune cell activity within the islets, allowing the remaining pancreatic islet β cells to resume functioning.

Altogether, the findings suggest a model in which blockade of IL-7 signaling by anti-IL-7R mAbs reduces both T cell activation and memory activity of cells that already are active (see Figure 1, "Blocking IL-7 in type 1 diabetes").

Results were published in the *Proceedings of the National Academy of Sciences*. Doms did not patent his findings. Pfizer has filed patents on its antibodies, and the IP is not available for licensing.

Doms said sustained activity by memory T cells is needed for type 1 diabetes progression. As a result, he said, blocking the activity of memory cells with anti-IL-7R antibodies might halt the course of the disease—even if considerable damage already has been done.

"Type 1 diabetes is perpetuated by a memory response, and diagnosis occurs late in the game when memory response has already arisen," said Doms. "When you go hyperglycemic, you still have about 10%–20% of the islet cell mass left," enough to sustain insulin production if the memory response can be halted.

Intervening with anti-IL-7R therapy in newly diagnosed patients might "preserve the islet mass that remains by eliminating memory

cell activity," he noted.

For patients with advanced disease, Doms thinks anti-IL-7R treatment could complement regenerative therapies that aim to restore β cell levels.

"A lot of people are investing in creating new islets, but if you don't stop the autoimmune response those cells will be destroyed again," he said.

Therapeutic prospects

The teams are now independently working out the mechanism of action of their IL-7R-blocking mAbs.

Doms and Lin think anti-IL-7R treatment is likely to alter the balance of stimulatory and inhibitory activity in T cells.

Lin's team found that T cells harvested from mice treated with anti-IL-7r mAbs had higher levels of Pd-1 receptor (Pdcd1; Pd-1; Cd279) than cells from mice given control mAbs. PD-1 inhibits T cell activity.

Indeed, treatment of diabetic mice with an anti-Pd-1 mAb blocked the beneficial effects of the anti-IL-7r antibodies. What remains less clear is how exactly IL-7 signaling goes awry in type 1 diabetes and whether modulating the pathway might have long-term consequences.

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—Hans Doms,
Boston University School of Medicine

Figure 1. Blocking IL-7 in type 1 diabetes. Lee *et al.* and Penaranda *et al.* have evidence that blocking IL-7 signaling can protect against type 1 diabetes.

IL-7 [a] normally engages the T cell membrane-associated IL-7 receptor (IL-7R; CD127) [b], leading to T cell proliferation and activity [c]. High T cell levels due to IL-7 signaling lead to potent immune activity against pathogens, but mutations thought to activate this pathway are linked with autoimmune disease [d]. Inhibitory IL-7R mAbs independently discovered by **Pfizer Inc.** and by researchers at the **University of California, San Francisco** block IL-7 signaling and arrest the progression of type 1 diabetes in mice. **Effimune S.A.S.** has the anti-IL-7R mAb MD707 in preclinical development for transplant rejection and a range of autoimmune indications.

David Booth, associate professor of immunogenetics at **The University of Sydney**, said prior mouse genetic studies suggest eliminating IL-7 activity outright could lead to lymphopenia.

"Inhibiting normal T cell functioning is a concern, given what happens when you knock out the IL-7 receptor," said Booth. "Knocking it down [with mAbs] could have very unpredictable results" depending on the potency of the anti-IL-7R knockdown.

"The biggest challenge and caveat is the immunosuppressive effect" of blocking IL-7 signaling, agreed Dooms. "To address this concern, our next step is to infect these animals with pathogens to see how immunosuppressed they really are."

Another question is whether IL-7 and its receptor have the same effects in mice and humans. Michael Demetriou, director of the

National Multiple Sclerosis Society Center for MS Comprehensive Care at the **University of California, Irvine**, said the biology of IL-7 signaling is quite complex and is likely to differ between the two species.

"We've looked at IL-7 in humans, and it does different things depending on what cell and what stage of immune cell development you're looking at," said Demetriou. "In early stages of T cells, it enhances growth and development, but in mature T cells it actually inhibits growth. It's not as simple as in mice, where if you knock IL-7 out you get lymphopenia and if you agonize it you get autoimmunity."

"I would be hesitant to put these mAbs into clinical trials until we get a better understanding of the differences between the human and mouse IL-7 systems," he added.

Indeed, Demetriou and Booth noted that in humans, the autoimmune disease-linked allelic variant of *IL-7R* encodes a protein that is likely to have lower activity than the wild-type form. Thus, it is possible that further lowering IL-7 signaling with antibodies against its receptor could worsen type 1 diabetes, not reverse it.

Lin said this possibility was merely speculative, noting that it is not yet known how the autoimmunity-associated IL-7R variant affects IL-7 signaling.

Angela Crawley, associate scientist at **Ottawa Hospital Research Institute**, said the best-case scenario for the anti-IL-7R strategy is that blocking the receptor would lead to a fairly subtle recalibration of the T cell response away from self antigens without perturbing other immune functions.

By blocking IL-7R, "it may be that you've raised the threshold for self antigens but not for pathogen-derived antigens," she said.

She added that other cytokines such as IL-15 and thymic stromal lymphopoietin (TSLP) also are thought to promote T cell memory response. Thus, she wanted to know how blocking those molecules combines with IL-7R blockade in diabetic mice.

Crawley added that the mouse data in the two papers helps build a case for trying the strategy in the clinic.

"If your goal is to prevent further destruction of the islets, this target should be high on your list," she said.

The UCSF and Pfizer teams' findings lend support to the anti-IL-7R strategy being pursued by **Effimune S.A.S.**

Chairman Maryvonne Hiance said the two teams' findings are in line with her company's data for MD707, the company's anti-IL-7R mAb, in preclinical models of other autoimmune indications.

"These two reports provide a strong scientific rationale and significance for anti-IL-7R immunotherapy as a unique strategy for patients with type 1 diabetes," said Hiance. "Very few strategies have been described to reverse established type 1 diabetes in NOD mice."

This month, Effimune reported positive preclinical data for MD707 in a mouse model of transplant.

Hiance said Effimune filed patents in 2011 on using anti-IL-7R mAbs to prevent transplant rejection and to treat a range of autoimmune conditions including type 1 diabetes, lupus and Crohn's disease.

A Pfizer spokesperson declined to disclose the development status of the mAbs described in Lin's study.

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REFERENCES

1. Penaranda, C. *et al. Proc. Natl. Acad. Sci. USA*; published online June 25, 2012; doi:10.1073/pnas.1203692109
Contact: Hans Dooms, Boston University School of Medicine, Boston, Mass.
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2. Lee, L.-F. *et al. Proc. Natl. Acad. Sci. USA*; published online June 25, 2012; doi:10.1073/pnas.1203795109
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3. Lundmark, F. *et al. Nat. Genet.* **39**, 1108–1113 (2007)
4. Todd, J.A. *et al. Nat. Genet.* **39**, 857–864 (2007)
5. Lee, L.-F. *et al. Sci. Transl. Med.* **3**, 93ra68 (2011)

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