EPO plays defense

By Lev Osherovich, Senior Writer

North American researchers have shown that erythropoietin can stave off the destruction of pancreatic islet β cells in mouse models of type 1 and type 2 diabetes.¹ Although erythropoietin itself is unlikely to become a diabetes therapy due to potential safety issues, the findings could add a new indication for tissue-protecting erythropoietin mimetics being developed by **Warren Pharmaceuticals Inc.**

Erythropoietin (EPO) initially was thought to act as a growth factor in the bone marrow to trigger proliferation of red blood cell precursors. Indeed, that hypothesis prompted **Amgen Inc.** to develop Epogen recombinant EPO, which was initially approved to treat anemia associated with chronic kidney disease (CKD) in 1989.

Now, some researchers suspect that EPO also can act as an anti-inflammatory or antiapoptotic factor at sites of stress and injury in other tissue.

"We all agree that EPO's main effect is to induce erythropoiesis," said Minna Woo, associate professor of medicine at the **University of Toronto** and the team's lead investigator. "But we and others have seen that EPO can have cytoprotective features including antiapoptotic, pro-proliferative and proangiogenic activity." The team included researchers from the **University of Nebraska Medical Center**, the David Geffen School of Medicine at the **University of California, Los Angeles**, the **Mount Sinai Hospital Joseph and Wolf Lebovic Health Complex** and **St. Michael's Hospital**.

Prior clinical work by others had found that dialysis patients receiving EPO had lower blood sugar than untreated controls,² suggesting a potential antidiabetic effect of EPO.

To prove this hypothesis, Woo's team tested the effect of recombinant human EPO on pancreatic islet β cell function in two mouse models of diabetes. In one model, a toxic chemical gradually destroyed the β cells, mimicking the autoimmune attack that causes type 1 diabetes. In the other model, a genetic defect in fat metabolism led to obesity, inflammation and β cell exhaustion—the hallmarks of type 2 diabetes.

In both models, EPO lowered fasting blood glucose and slowed the loss of β cell mass compared with saline.

Woo's team then delved into the mechanism of EPO's effect on β cells and found that the growth factor activated expression of antiapoptotic genes. The team then knocked out Janus kinase-2 (JAK-2), a signaling molecule known to mediate the antiapoptotic effects of cytokines. In those mice, compared with wild-type controls, EPO did not have antidiabetic effects.

Data were published in *The Journal of Experimental Medicine*.

"This study shows that β cells can be protected from chemical or autoimmune toxicity," said Pietro Ghezzi, professor of experimental medicine at **Brighton and Sussex Medical School**.

Warren Therapeutics CSO Michael Brines added that Woo's study delivers *in vivo* evidence for a direct protective effect of EPO on β cells.

"Earlier work has shown that islets isolated for transplantation could be protected [*in vitro*] by EPO," said Brines. He noted that several recent preclinical studies "have shown profound effects of EPO on glucose homeostasis and fatty acid metabolism, pointing to really large effects on the diabetic state."

Brines told SciBX that Woo's work provides a rationale for clinical development of EPO derivatives for metabolic disease.

"There's a lot of interest in expanding β cell mass to treat diabetes," said Brines. He added that according to Woo's study, "EPO appears to have a very significant effect" on β cell levels.

Woo, Brines and Ghezzi agreed that using EPO itself as a diabetes therapy would be ill-advised because of safety concerns. Foremost among these are the long-term effects of red blood cell overproduction.

"This study is not saying that we should take EPO to protect against diabetes," said Woo. "The elephant in the room is that EPO will still promote erythropoiesis."

Previous clinical studies also have raised concerns about cancer and cardiovascular risks from chronic EPO treatment.³ Ghezzi noted that, due to

its proangiogenic and antiapoptotic effects, EPO can promote tumor growth in patients already harboring cancer cells. In recent years, the FDA imposed a black box warning on the label of EPO drugs and a REMS for cancer patients receiving two EPO products from Amgen—Epogen epoetin alfa and Aranesp darbepoetin alfa—and on Procrit epoetin alfa from **Johnson & Johnson**.⁴

"For diabetes you would need chronic, systemic administration of EPO," said Ghezzi. "There are some safety issues associated with

increased risk of thrombosis and cancer growth. The way to go is to make derivatives of EPO, like what Warren is doing."

Warren is developing EPO derivatives for uses outside of the bone marrow as tissue protectants. In 2002, Warren out-licensed a carbamylated form of EPO to **H. Lundbeck A/S** for neurological indications. That compound, now called Lu AA24493, is in Phase I testing for Friedrich's ataxia and in Phase II testing for acute ischemic stroke.

Lundbeck declined to comment on the potential of Lu AA24493 in diabetes.

Warren's EPO mimetics are being developed through a wholly owned subsidiary, Araim Pharmaceuticals Inc. Brines said that Araim was spun out of Warren to develop peptide therapeutics while Warren continues developing biologics.

"We have developed peptide derivatives that have no primary structural homology to EPO but recapitulate its 3D structure," said Brines, who is also CSO of Araim.

"This study is not saying that we should take EPO to protect against diabetes. The elephant in the room is that EPO will still promote erythropoiesis."

**—Minna Woo,
University of Toronto**

Araim's lead compound, ARA-290, has completed Phase I testing, and the company is "now discussing which indication to pursue," Brines said.

EPOlogue

One outstanding question is whether EPO's effects in the pancreas are mediated through the same receptor as its erythropoietic effects.

Ghezzi said that one school of thought maintains the EPO receptor is present in a range of tissues but requires a higher dose of EPO to elicit tissue protective effects than is needed to trigger erythropoiesis in the bone marrow. Other researchers suspect that EPO's effects outside the bone marrow are mediated by different receptors.⁵

Last year, Amgen scientists published evidence in *Blood* that EPO receptors are absent in nonerythropoietic cell lines,⁶ consistent with the latter view. Amgen declined to comment on the Woo study but cited the *Blood* paper as an argument against any peripheral effects of EPO.

However, Woo's team found that EPO had only a modest β cell-protecting effect in mice with a pancreas-specific deletion of the EPO receptor. Thus, Woo thinks that, at least in the pancreas, targeting the EPO receptor would be a reasonable strategy.

She now hopes to collaborate with Brines to test ARA-290 in mouse models of diabetes and to confirm that such a strategy would not elicit cancer or cardiovascular effects like thrombosis.

Woo did not patent her findings.

Osherovich, L. *SciBX* 4(2); doi:10.1038/scibx.2011.35
Published online Jan. 13, 2011

REFERENCES

1. Choi, D. *et al. J. Exp. Med.*; published online Dec. 13, 2010; doi:10.1084/jem.20100665
Contact: Minna Woo, University of Toronto, Toronto, Ontario, Canada e-mail: mwoo@uhnres.utoronto.ca
2. Drüecke, T.B. *et al. N. Engl. J. Med.* **355**, 2071–2084 (2006)
3. Edelson, S. *BioCentury* **15**(12), A1–A7; March 12, 2007
4. Usdin, S. *BioCentury* **18**(9), A12–A13; Feb. 22, 2010
5. Brines, M. & Cerami, A. *Nat. Rev. Neurosci.* **6**, 484–494 (2005)
6. Sinclair, A.M. *et al. Blood* **115**, 4264–4272 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Brighton and Sussex Medical School, Brighton, U.K.
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Mount Sinai Hospital Joseph and Wolf Lebovic Health Complex, Toronto, Ontario, Canada
St. Michael's Hospital, Toronto, Ontario, Canada
University of California, Los Angeles, Calif.
University of Nebraska Medical Center, Omaha, Ne.
University of Toronto, Toronto, Ontario, Canada
Warren Pharmaceuticals Inc., Westchester, N.Y.