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Liver X receptor marks the spot

By Lev Osherovich, Senior Writer

Multiple companies have shelved liver X receptor agonists for cardiovascular indications because of unfavorable effects on lipid levels. Now, a New York team and **Rgenix Inc.** have found a different role for the agonists in metastatic melanoma.[1]

The group, led by **The Rockefeller University** assistant professor Sohail Tavazoie, came upon the nuclear hormone receptor as a melanoma target while studying the effect of apolipoprotein E (APOE) on cancer metastasis.

APOE is the protein component of cholesterol-carrying lipoprotein particles.

"Zelboraf and Yervoy work in about half of patients, but with our APOE activation therapy, there is response across all tumor types, even tumors that have developed resistance to targeted therapies."
—Sohail Tavazoie, The Rockefeller University

In 2012, Tavazoie's team discovered that Apoe produced by noncancerous tissue combats melanoma vascularization and metastasis.[2]

"In our previous paper we used an unbiased approach to show that Apoe suppresses metastasis of melanoma cells," said Tavazoie. The tricky part, he said, was figuring out how to elevate Apoe levels.

In the new study, Tavazoie's team tested the hypothesis that liver X receptor (LXR) agonists, which are known to increase APOE levels, would have a beneficial effect in melanoma.

"The idea was to use the cell's machinery to make more APOE in the stroma," said Tavazoie.

The findings present repurposing opportunities for shelved LXR agonists, including tool compounds originally developed by **GlaxoSmithKline plc** and Tularik Inc., which was acquired by **Amgen Inc.** in 2004.

Those compounds hit both isotypes of LXR—LXR-β (NR1H2) and LXR-α (NR1H3)—as well as the related retinoid X receptor (RXR). The molecules raised triglyceride levels in rodents and did not advance into clinical development.

Metastasis stasis

Tavazoie's team used tool compounds and a variety of cell culture and mouse models to make the case for agonizing LXR-β to treat melanoma.

In vitro, nonselective LXR agonists prevented invasion and endothelial recruitment, two key traits of metastatic tumors. In several mouse models of melanoma, oral LXR agonists prevented metastasis to the brain and lung and increased survival compared with vehicle controls.

"When we fed mice with these drugs, we found that they strongly suppressed melanoma growth and metastasis," said Tavazoie. "We see 30-fold reductions in metastasis."

shRNA knockdown or antibody depletion of APOE blocked the beneficial effects of LXR agonists, indicating that the treatment likely worked by inducing the expression of APOE.

The team then used genetics to determine that somatic LXR-β was the key target for preventing melanoma metastasis.

In *Lxr-β* knockout mice, tumors did not respond to nonselective LXR agonists. Mice lacking *Lxr-α* responded comparably to wild-type mice with tumors. Thus, the team concluded that activation of LXR-β but not LXR-α in normal tissue surrounding a tumor could combat metastasis.

Tavazoie thinks that raising APOE levels with LXR-β agonists is an attractive option for melanomas as an adjunct to targeted therapies that directly block tumor cell division.

Marketed melanoma therapies include Zelboraf vemurafenib, a selective BRAF inhibitor from **Roche**, **Chugai Pharmaceutical Co. Ltd.** and **Daiichi Sankyo Co. Ltd.**, and Yervoy ipilimumab, a human mAb against CTLA-4 (CD152) from **Bristol-Myers Squibb Co.**

Indeed, the team found that a combination of LXR agonists with Zelboraf or a CTLA-4 antibody enhanced the drugs' effects on tumor metastasis and increased survival in mice compared with Zelboraf or CTLA-4 antibody alone. The combination also worked in mice with tumors resistant to Zelboraf.

"Zelboraf and Yervoy work in about half of patients, but with our APOE activation therapy, there is response across all tumor types, even tumors that have developed resistance to targeted therapies," said Tavazoie, who is also cofounder and chair of the scientific advisory board at Rgenix.

Results were reported in *Cell* and are covered by pending patents licensed to Rgenix.

LXR revival

The challenge to using LXR agonists in melanoma is getting selectivity for LXR-β while avoiding cardiovascular liabilities.

Rgenix CEO David Darst said that the company in-licensed a portfolio of patents late last year from an undisclosed pharma covering composition of matter for a family of LXR agonists.

"Our lead candidate is chemically related to one of the compounds used in the paper" but has undergone optimization to improve its selectivity for LXR-β, said Darst. "We're in the process of conducting a dose range–finding toxicity study in monkeys."

Darst said that the company plans to be in the clinic by the first half of 2015.

At least one other company—**Vitae Pharmaceuticals Inc.**—has LXR-β-selective compounds in development. Vitae's compounds are in preclinical testing for atherosclerosis and atopic dermatitis. CSO Richard Gregg said that Vitae's LXR agonists are highly selective for LXR-β and

thus have a more favorable effect on lipid levels than pan-LXR agonists.

"LXR has been around as a target for a long time, about 10 years or so, but there have been certain problems of selectivity and lipid elevation," said Gregg. "I don't believe there are many active programs going on right now. People have largely dropped out of this space."

Tavazoie's study suggests that LXR agonists could "have a very positive impact, inhibiting growth and metastasis" of melanoma, said Gregg. "The downside is that LXR agonists have a tendency to induce lipid synthesis, leading to increased circulating triglycerides and fat accumulation in the liver."

"For atherosclerosis, this is a big downside, but for tumors these side effects are better accepted," said Gregg. "If a cancer is going to kill you in six months, elevated triglycerides are not as much of a concern."

Tavazoie said that the lipid-altering effects of LXR agonists are transient.

"Previous compounds have been shown to cause an acute increase in levels of triglycerides, but this goes away," said Tavazoie. "This should not be a concern for melanoma patients."

Rgenix was formed in 2010 to develop therapies for metastatic cancer coming out of Tavazoie's lab. The company also has mAbs for triple-negative breast cancer, including an antibody that targets insulin-like growth factor binding protein 2 (IGFBP2). Rgenix hopes to partner its mAbs and is focused on internal development of its small molecules.

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