Going APOA1 in cancer

By Steve Edelson, Executive Editor

Researchers at the **University of California, Los Angeles** and colleagues have shown that apolipoprotein A-1, the major component of high-density lipoprotein, could have a therapeutic effect in ovarian cancer.¹ **Resverlogix Corp.**, a biotech with an apolipoprotein A-1 program in cardiovascular disease, is considering out-licensing options for oncology based on the findings.

Apolipoprotein A-1 (APOA1) is a key component of the reverse cholesterol transport pathway. The lipoprotein removes cholesterol from cells in the periphery and helps shuttle it to the liver, where cholesterol is excreted. Given APOA1's role in cholesterol-related disorders such as atherosclerosis, companies pursuing APOA1 or its mimics in the cardiovascular space include two sets of biotech-pharma partners.

On top of its cholesterol transport function, APOA1 also has been shown to bind to proinflammatory phospholipids, which give it anti-inflammatory properties.² Those findings provided the hint that APOA1 could be therapeutic in cancer, as some phospholipids—the lysophospholipids—can prompt cancer cells to start growing.

Indeed, APOA1's potential involvement in ovarian cancer does not come as a complete surprise—the protein is one of the biomarkers measured by the Oval Test from **Vermillion Inc.** and **Quest Diagnostics Inc.** The *in vitro* diagnostic multivariate index (IVDMIA) test is used to help assess the likelihood that an ovarian mass is benign or malignant.

What was unknown was whether APOA1 is correlative or causative in the disease.

A UCLA-led team suspected the latter. “Because lipid transport, inflammation, and oxidative stress are associated with the development and progression of cancer, we hypothesized that the reduced levels of apoA-I in ovarian cancer patients may have been causal in disease progression,” the group wrote in a paper published in the *Proceedings of the National Academy of Sciences*.

In addition to UCLA, the article included researchers from **The University of Alabama at Birmingham**.

To answer their question, the researchers first generated transgenic mice overexpressing human APOA1. Those animals survived significantly longer than wild-type littermates following an injection of ovarian cancer cells ($p < 0.0001$). The increase in survival was accompanied by a significant decrease in the development of tumors compared with that in controls ($p < 0.01$).

Next, the researchers used a pair of compounds from **Bruin Pharmaceuticals Inc.**, a biotech formed by UCLA and UAB to develop APOA1 peptide mimics. The oral and subcutaneous mimics decreased ovarian tumor burden in mice compared with a scrambled peptide.

Patents covering the peptide mimics described in *PNAS* are licensed to Bruin from UCLA and UAB. In 2005, Bruin licensed the mimetics to **Novartis AG**. The pharma did not return calls seeking comment on the program.

Mechanism still unknown

The precise mechanism by which APOA1 elicited its positive effects remains unclear. The researchers did show that apoptosis is not the culprit. Instead, they suspect that APOA1's removal of lysophosphatidic acid (LPA) leads to inhibition of cell growth.

“What I suspect is happening is we're taking away an important growth factor—LPA—from these immunocompetent mice,” noted Alan Fogelman, executive chair of the Department of Medicine and director of the atherosclerosis research unit at UCLA's David Geffen School of Medicine. “I think the peptide mimics are tilting the battle between the immune system and the tumor in favor of the immune system by removing this potent promoter” of tumor formation.

“These are very interesting findings. The results come from the proteomics of APOA1 being a cancer risk factor, and the data fit with the mechanism of reverse cholesterol transport being anti-inflammatory,” said Jan Johansson, SVP of medical affairs at Resverlogix. “It's possible that you could take a compound like ours and test its effects in ovarian cancer with other compounds” such as chemotherapeutics.

Resverlogix's RVX-208, an APOA1 transcription enhancer, is in Phase II testing to treat atherosclerosis in patients with acute coronary artery disease (CAD). Data are expected this month.

Because the company is focused on cardiovascular disease, President, CEO and cofounder Donald McCaffrey told *SciBX* that Resverlogix would be interested in licensing out rights to the compound in cancer. “We've kept up on the alternate uses of APOA1 in other diseases, but we're very focused on our cardio program,” he said.

Roche's Michael Pech, section head for metabolic diseases, agreed that the findings in the *PNAS* article are intriguing but added that “whether we'd follow that initial finding and explore our APOA1 mimetic program in cancer, I can't say yet.”

In February, Roche partnered with **Artery Therapeutics Inc.** to co-develop the biotech's APOA1 peptide mimetics. The lead compound, AT5261, is in preclinical testing and is being developed to treat atherosclerosis and prevent cardiovascular events in patients who have suffered a heart attack or stroke.

Pech told *SciBX*: “Looking at the *PNAS* paper, I don't know yet what a dose response would look like. In general, a challenge for APOA1 is that you might need quite large doses of the protein.”

He also said that UCLA's planned mechanistic studies of APOA1 in ovarian cancer will be essential. “The finding seems to be affecting the proliferation rate of tumors but not apoptosis. Later in clinical development people will be very interested in the mechanism.”

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COMPANIES AND INSTITUTIONS MENTIONED

Artery Therapeutics Inc., Danville, Calif.
Bruin Pharmaceuticals Inc., Los Angeles, Calif.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Quest Diagnostics Inc. (NYSE:DGX), Madison, N.J.
Resverlogix Corp. (TSX:RVX), Calgary, Alberta, Canada
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
The University of Alabama at Birmingham, Birmingham, Ala.
University of California, Los Angeles, Calif.
Vermillion Inc. (NASDAQ:VRML), Austin, Texas