PPARD's colon cancer conundrum

By Lauren Martz, Staff Writer

Work by a team from **The University of Texas M.D. Anderson Cancer Center** adds one more experiment showing that knocking out PPARD can slow colon cancer progression.¹ But with other research suggesting the opposite effect, whether it's better to up- or downregulate PPARD to treat colon cancer isn't likely to be resolved soon. To help answer the question, researchers suggest two tacks: repeating the latest experiment in different animal models and blocking the target with PPARD antagonists.

Peroxisome proliferation-activated receptor- δ (PPARD; PPAR δ) has been extensively studied in metabolic diseases. Companies with PPARD agonists in clinical development include **sanofi-aventis Group**, whose SAR351034 is in Phase I testing for dyslipidemia and diabetes, and **Cerenis Therapeutics S.A.**, which has CER-002 in Phase I testing for atherosclerosis.

Although the effect of agonizing PPARD is well understood in metabolic disease, the function of the receptor in cancer is not well understood, and PPARD antagonists have not been well studied.

Interest in PPARD modulation in colon cancer stems from work showing that the receptor is overexpressed in both human colon cancers and experimentally induced colon tumors in mice.²

Other studies have also shown that activating PPARD with a synthetic ligand could increase intestinal tumorigenesis³ and that inhibiting PPARD expression with NSAIDs could prevent the development of colon cancer.⁴

However, in other studies, inactivating PPARD through an exon 4 germline deletion in mice had no effect,⁵ whereas deleting the receptor's exon 8 increased tumorigenesis.⁶

Imad Shureiqi, associate professor in the Department of Clinical Cancer Prevention at M.D. Anderson, and a team of colleagues thought the conflicting results might be due to the use of mice with inconsistent genetic backgrounds, the methods used to induce tumorigenesis and the methods of PPARD targeting and knockout. They thus developed a modified model that might better represent the human condition.

As reported in the *Journal of the National Cancer Institute*, the team disrupted PPARD expression specifically in the colonic epithelium of FVB/N mice, which are highly susceptible to chemical-induced cancers, to show that this could significantly reduce colonic tumorigenesis.

Mice with a homozygous genetic deletion of PPARD exon 4 specifically in colonic epithelial cells had fewer colon adenocarcinomas than wild-type mice or mice with a heterozygous deletion when given an intraperitoneal injection of azoxymethane (AOM). PPARD^{-/-} mice developed an average of 0.1 tumors at 20 weeks after the last AOM injection, PPARD^{+/-} mice developed an average of 0.2 tumors and wild-type mice developed an average of 6.6 tumors.

Also, although the angiogenesis-promoting VEGF was upregulated in tumors, its increase was less pronounced in PPARD^{-/-} mice. VEGF levels were higher in heterozygous mice and still higher in wild-type rodents.

Ideal model

Although Shureiqi and colleagues wrote in *JNCI* that they believe their tissue-specific model is better than germline knockout of PPARD via deletion of exon 4 or exon 8, researchers interviewed by *SciBX* think that repeating the study in mice of different genetic backgrounds, with different methods of inducing colon cancer, and conducting studies in human samples are both necessary to confirm the team's results.

"Essentially I think more studies need to be performed in different animal models, animals with different genetic backgrounds, as well as to start to look more in human tissue to see whether the findings are likely to translate," said David Bishop-Bailey, a senior lecturer at **Queen Mary, University of London**.

Indeed, according to Jeffrey Peters, professor in the Department of Veterinary and

Biomedical Sciences of the Center for Molecular Toxicology and Carcinogenesis at **The Pennsylvania State University**, "we did the same experiment and found the exact opposite results in mice with a different genetic background. It begs the question whether these mouse models will represent the human disease at all."

This view was echoed by Charles McWherter, SVP of research and preclinical development at **Metabolex Inc.** "Knockout mouse models can be very useful for delineating the roles of proteins in specific diseases. However, there are caveats to such studies. One of these is the tendency for many such knockout results to be consistent in only certain mouse strains," he said.

He added: "The results of the paper should be tested by backcrossing to other strains to address the possibility."

Metabolex's MBX-8025, a PPARD agonist, is in Phase II testing to treat dyslipidemia.

McWherter also noted that "another caveat to the current study is the likelihood that the complete absence of a nuclear receptor hormone, such as PPARD, is probably quite different than the presence of an antagonist-bound receptor protein. Nuclear hormone receptor proteins can play roles as DNA-bound scaffolds and repressors in certain contexts that may have little to do with the specific effects of ligands when bound to the same receptor."

As a result, McWherter said, "the only way that one could be certain whether antagonists, or possibly agonists, of PPARD are able to

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—Jeffrey Peters,
The Pennsylvania State University

prevent or treat tumors would be to test specific compounds in animals.”

Gideon Bollag, SVP of research at **Plexxikon Inc.**, agreed that the next step is to identify and test a pure antagonist to understand how therapeutic targeting will affect the receptor.

Plexxikon's PLX204, a PPAR pan-agonist, is in Phase II testing to treat type 2 diabetes.

McWherter added that the method of tumor induction doesn't parallel human cancer and thus might not be the best model. He noted that the study “relied on a chemical carcinogenesis model, whereas colorectal carcinoma is believed to have a strong causal component from chronic inflammation and underlying genetic factors.”

The *JNCI* authors also suggested the results could be stronger if the PPARD knockout was repeated in the entire colon rather than the epithelial cells specifically, because the receptor might function differently in different cell types.

Side effects

Assuming that sufficient evidence is collected to show that antagonizing PPARD could treat or prevent colon cancer, potential toxicity would be the next important consideration.

Because activation of PPARD improves metabolic function, researchers interviewed by *SciBX* voiced concerns that inactivating it could have negative consequences.

“As far as I am aware, only one selective antagonist has been described, and we just don't know what systemic effects it has *in vivo* or in man. This is a major concern as it appears that drug companies' interest and much academic research has been in the development of PPARD agonists for dyslipidemia,” Bishop-Bailey said. “PPARD antagonists may therefore have severe metabolic side effects—whether they do or how they would limit its use in cancer therapy is just not known.”

Bollag agreed. “Agonists have beneficial effects, so it is possible that an antagonist might work the other way and counter the beneficial

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—Gideon Bollag, *Plexxikon Inc.*

effects in metabolic diseases,” he said.

Indeed, it is the pleiotropic nature of the receptor that has caused companies to shy away from targeting PPARD therapeutically. Because of this, McWherter noted, “the FDA requires all sponsors of PPAR agents to complete two-year carcinogenicity studies prior to long-term dosing in humans.”

Despite the hurdles in both confirming how PPARD works and developing a safe therapeutic, the researchers contacted by *SciBX* think it is still worth pursuing.

“It's always advantageous in cancer to have a therapeutic with a completely new mechanism; therefore, PPARD antagonists are very interesting,” Bollag said. “A role for PPARD modulators in cancer is definitely there, but it just hasn't been developed yet.”

Shureiqi told *SciBX* that the findings have not been patented or licensed.

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COMPANIES AND INSTITUTIONS MENTIONED

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