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## PRODUCT R&D

# TEMPEST TAKES PPAR ALPHA INTO CANCER

By Lauren Martz, Senior Writer

Tempest Therapeutics Inc.'s first data from its preclinical PPAR $\alpha$  program gave it the support it was looking for to repurpose the cardiovascular target for cancer.

Tapping into the emerging field of cancer immuno-metabolism, Tempest is moving beyond IDO with a target that acts via a different mechanism and controls cancer cells in addition to immune cells.

The biotech stumbled onto PPAR $\alpha$ 's role in cancer via an undisclosed academic collaborator.

At the 2018 Society for Immunotherapy of Cancer (SITC) meeting, Tempest presented data showing its PPAR $\alpha$  antagonist TPST-1120 induced tumor regression and extended survival in mouse models of cancer.

The target joins a list of metabolic proteins that could be modulated to help the immune system shut down cancer. While metabolic processes have long been a focus in cancer, immuno-metabolism operates at the intersection of cancer metabolism and immuno-oncology and aims to control metabolic processes in immune cells to promote their antitumor activity (see ["Raising Metabolism"](#)).

Tempest emerged from Versant Ventures' Inception Sciences Inc. incubator in March with a \$70 million series B round to develop small molecules that modulate antitumor immunity pathways.

The company abandoned its lead IDO program following the Phase III failure of Incyte Corp.'s IDO1 antagonist epacadostat in April. In the ECHO-301 study, epacadostat plus Merck & Co. Inc.'s Keytruda pembrolizumab missed the primary endpoint of improving progression-free survival (PFS) vs. Keytruda alone in first-line metastatic melanoma.

"There's no doubt that the failure of epacadostat really brought that target into question, and it isn't our goal to revalidate IDO as a target," Tempest President and CEO Tom Dubensky told BioCentury.

PPAR $\alpha$  is well-known as a target in cardiovascular disease, where at least twelve companies market PPAR $\alpha$  agonists to treat dyslipidemia, hypercholesterolemia and hypertriglyceridemia. The agonists increase uptake and processing of lipids by adipocytes and other cell types.

In cancer metabolism, Tempest's antagonist would have a first-in-class advantage; its goal is to block lipid metabolism in the tumor microenvironment by inhibiting rather than activating PPAR $\alpha$ .

Tempest has not directly compared efficacy of its PPAR $\alpha$  inhibitor with any IDO inhibitors.

Tempest plans to submit an IND for TPST-1120 this year and begin a Phase I/Ib trial in 13-14 different cancers early next year.

## IMMUNE REPOLARIZATION VIA PPAR ALPHA

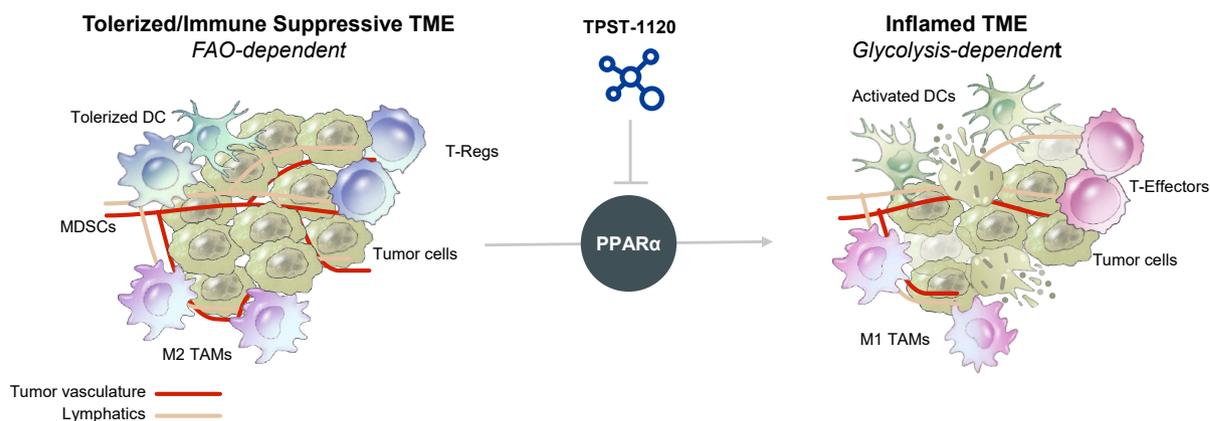
Tempest Therapeutics Inc. is stepping into cancer immuno-metabolism with a first-in-class PPAR $\alpha$  antagonist that attacks tumors in two ways: by disrupting a metabolic pathway that certain cancer cells rely on for energy, and by shifting immune cells in the tumor microenvironment (TME) from a suppressive to an effector phenotype. The latter mechanism is depicted below.

In a **tolerized/immune suppressive TME**, immune cells are polarized toward an immunosuppressive phenotype reliant on fatty acid oxidation for metabolism. The **FAO-dependent** cells include tolerized dendritic cells (DCs), myeloid-derived suppressor cells (MDSCs), M2 tumor-associated macrophages

(TAMs) and Tregs.

Tempest's PPAR $\alpha$  inhibitor TPST-1120 repolarizes the cells to an effector phenotype by shifting their metabolism to become **glycolysis-dependent**. PPAR $\alpha$  is a transcription factor that promotes expression of genes required for fatty acid oxidation; its inhibition makes the cells no longer dependent on the FAO pathway. The resulting effector T cells, M1 macrophages and activated dendritic cells promote antitumor immunity in the inflamed TME. *Source: Tempest Therapeutics Inc.*

PPAR $\alpha$  - Peroxisome proliferation activated receptor  $\alpha$



### AGAINST HIJACKING

PPAR $\alpha$  is a transcription factor that regulates the expression of a set of genes required for fatty acid oxidation, a metabolic process used by cells to create energy.

According to Dubensky, it's well established that as tumors evolve and metastasize, they hijack metabolic pathways. In some suppressive immune cell populations, he said, the fatty acid oxidation pathway is a key process that becomes co-opted to the tumor's benefit.

At SITC, Tempest showed that TPST-1120 cuts off the energy supply of cancer cells that rely on fatty acid oxidation, inhibiting proliferation. Unpublished data show the antagonist also can repolarize M2 macrophages in the tumor microenvironment to a proinflammatory M1 phenotype (see "Figure: Immune Repolarization via PPAR Alpha").

As monotherapy, TPST-1120 decreased tumor growth in mouse models of colon cancer and melanoma, compared with vehicle.

Tempest built in a combination strategy from the start and tested TPST-1120 plus chemotherapy and checkpoint inhibitors, which Dubensky noted are "natural and rational combinations" for the antagonist based on its mechanism of action.

"Tumors resistant to chemotherapy are known to up-regulate fatty acid oxidation, and fatty acid oxidation up-regulates PD-1," he said.

In a mouse model of pancreatic cancer, TPST-1120 plus gemcitabine extended survival through day 200, whereas mice treated with vehicle or either agent alone all died by day 32.

Similarly, mice treated with TPST-1120 plus an anti-PD-1 mAb, but not animals treated with either agent alone, survived past 24 days in a mouse model of colon cancer. Three out of the 15 mice that received the combination therapy were tumor-free 60 days after stopping the therapy and remained tumor-free after rechallenge with more cancer cells.

The antagonist had no therapeutic effect in mice lacking STING or BATF3, which are involved in innate immune signaling and

dendritic cell development, respectively, suggesting TPST-1120's mechanism requires multiple types of immune signaling. Tempest also showed TPST-1120's antitumor activity required the matrix glycoprotein TSP-1. TPST-1120 boosted TSP-1 levels in the tumor microenvironment, which the company believes interrupts a "don't eat me signal" on tumor cells and inhibits angiogenesis. Dubensky thinks the effects of TPST-1120 on TSP-1 lie downstream of PPAR $\alpha$  inhibition, and the company is conducting experiments to define the mechanism.

**"The failure of epacadostat really brought that target into question, and it isn't our goal to revalidate IDO as a target."**

Tom Dubensky, Tempest

Tempest plans to evaluate the molecule in the clinic in cancers with a high density of PPAR $\alpha$  expression and fatty acid oxidation, which include triple-negative breast cancer (TNBC), bladder cancer, hepatocellular carcinoma, renal cell carcinoma and prostate cancer.

CMO Ginna Laport said the company plans to track lipid levels in patients to make sure they don't increase to unsafe levels. Because agonizing the receptor decreases lipid levels, it's possible that antagonizing it could increase serum lipids.

Laport noted that the company hasn't seen any "striking" increases in serum lipid levels in preclinical models. She thinks the long history of PPAR $\alpha$  agonists will benefit Tempest's clinical development program.

"PPAR $\alpha$  is already being targeted in the clinic, so we know what biomarkers to measure to see if there is any effect on lipids in peripheral blood," she said.

#### COMPETING IN CANCER IMMUNO-METABOLISM

At least three other companies have attempted hitting other targets in the fatty acid oxidation pathway.

3-V Biosciences Inc. is developing an inhibitor of the enzyme FASN, which is required for fatty acid synthesis. The compound is in Phase I testing for solid tumors.

FASgen Inc. was also developing a FASN inhibitor for cancer, but the company is no longer active.

According to Dubensky, PPAR $\alpha$  inhibition provides broader control over fatty acid oxidation than inhibition of any one of its target genes.

"We believe blocking PPAR $\alpha$  is a better approach, because this transcription factor also induces the expression of FASN and other lipogenesis genes, in addition to the genes required for fatty acid oxidation metabolism," said Dubensky.

In the fatty acid oxidation pathway, PPAR $\alpha$  also controls expression of FGF21, PDK4, CD36 and CPT1A. According to BioCentury's BCIQ database, no companies have active programs against those targets.

Medigene AG discontinued development of its CPT1A inhibitor Etomoxir for congestive heart failure after the compound failed a Phase II trial in 2002.

Beyond IDO and PPAR $\alpha$ , other key targets in cancer immunometabolism are in the adenosine and glutamine pathways.

Tumor cells produce adenosine, which signals through receptors on effector immune cell surfaces to suppress activity. At least 22 companies have compounds targeting the pathway for cancer.

Like PPAR $\alpha$ , glutamine both feeds an energy pathway in tumor cells and exerts an immunosuppressive effect on immune cells.

Calithera Biosciences Inc.'s Phase II candidate CB-839 blocks the glutamine-metabolizing enzyme GLS, and Dracen Pharmaceuticals Inc. has preclinical antagonists of GLS and nine other glutamine-metabolizing enzymes. Dracen raised \$40 million in a tranced series A round led by Deerfield Management in March.

According to BioCentury's BCIQ database, no other companies are antagonizing PPAR $\alpha$  for cancer.

Genfit S.A. published preclinical data in June showing elafibranor (GFT505), a dual PPAR $\alpha$ /PPAR $\delta$  agonist in Phase III testing for non-alcoholic steatohepatitis (NASH), also had antitumor effects in the liver. Genfit did not respond in time for publication to an inquiry about whether it plans to pursue the compound for cancer.

Tempest CBO Alicia Levey said Tempest is "not surprised" that Genfit saw reduced development of HCC. "HCC is often a long term consequence of NAFLD/NASH progression where long-term underlying disease and inflammation contributes to the development of cancer," she said. "We are unaware of any data showing tumor shrinking effects of elafibranor."

#### FIRST-IN-CLASS LINEUP

Next up for Tempest is a potential first-in-class dual inhibitor of two receptors in the prostaglandin pathway: PTGER2 and PTGER4.

At least six other companies have PTGER4 inhibitors in development for cancer, all either in preclinical or in Phase I testing. Tempest's is the only one to target PTGER2. In immune cells, activation of the PTGER receptors decreases antitumor effector cell activity and increases suppressor cell activity.

Tempest's PTGER2/4 program is slated to enter the clinic by the end of 2019.

"We believe that by antagonizing both receptors, there is a synergistic effect in relieving prostaglandin induced immunosuppression of antitumor effector cells including dendritic cells and M1 macrophages," said Dubensky.

Tempest also is working on an undisclosed innate immune agonist, for which it expects to have preclinical validation data by the end of 2019.

The company expects its series B funding to last through mid-2020. Levey said the company is open to partnerships and may start actively seeking partners "once we have proof-of-mechanism data emerging from the clinic." ■

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#### COMPANIES AND INSTITUTIONS MENTIONED

3-V Biosciences Inc., Menlo Park, Calif.

Calithera Biosciences Inc. (NASDAQ:CALA), South San Francisco, Calif.

Dracen Pharmaceuticals Inc., Baltimore, Md.

Genfit S.A. (Euronext:GNFT), Loos, France

Incyte Corp. (NASDAQ:INCY), Wilmington, Del.

Medigene AG (Xetra:MDG1), Martinsried, Germany

Merck & Co. Inc. (NYSE:MRK), Kenilworth, N.J.

Tempest Therapeutics Inc., San Francisco, Calif.

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#### TARGETS

BATF3 - Basic leucine zipper ATF-like transcription factor

CD36 (GPVI)

CPT1A (CPT1) - Carnitine palmitoyl transferase 1

FASN (FAS) - Fatty acid synthase

FGF21 - Fibroblast growth factor 21

GLS - Glutaminase

IDO (INDO) - Indoleamine 2,3-dioxygenase

IDO1 - Indoleamine 2,3-dioxygenase 1

PD-1 (PDCD1; CD279) - Programmed cell death 1

PDK4 - Pyruvate dehydrogenase kinase 4

PPAR $\alpha$  - Peroxisome proliferation activated receptor  $\alpha$

PPAR $\delta$  - Peroxisome proliferation activated receptor  $\delta$

PTGER2 (Prostanoid EP2 receptor) - Prostaglandin E2 receptor EP2 subtype

PTGER4 (Prostanoid EP4 receptor) - Prostaglandin E2 receptor EP4 subtype

STING (TMEM173) - Transmembrane protein 173

TSP-1 (THBS1) - Thrombospondin-1

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