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EMERGING COMPANY PROFILE

YAP OFF, YAP ON

By Michael Leviten, Senior Writer

Vivace Therapeutics Inc. exploits opposite angles of the Hippo-YAP pathway, with first-in-class inhibitors that turn it off in cancers with activating mutations and activators that turn it on to enhance tumor immunogenicity in other cancers. The newco emerged from stealth mode this summer after closing a \$25 million Series B led by China-based Cenova Capital.

The Hippo-YAP pathway regulates cell growth and survival. Under normal conditions, Hippo signaling phosphorylates YAP1 and silences it. But under cellular stress, G-protein signaling dephosphorylates YAP1, triggering its translocation to the nucleus where it induces expression of survival genes.

Several cancers co-opt the pathway for survival and proliferation. About 85% of uveal melanomas have activating mutations in the G-proteins GαQ and GNA11, 70% of mesotheliomas have activated YAP1, and YAP1 gene amplifications occur in about 25% of all lung, cervical and thyroid cancers.

Because the pathway has been difficult to drug, Vivace took a target-agnostic approach in undisclosed cancer cell lines to identify pathway inhibitors. “We are studying tumors that are addicted to the pathway,” said CSO Leonard Post.

The approach led to compounds of undisclosed potency that turned the pathway off, some of whose targets were already known. “So it is druggable but, it was not obvious what to drug,” Post said.

CEO Sofie Qiao said Vivace’s *in vivo* testing will help it select a lead inhibitor of an undisclosed target by mid-2018. The company expects to submit an IND for a range of tumor types with YAP pathway mutations, such as uveal melanoma and mesothelioma, in 2019.

Array BioPharma Inc. and partners have the MAP kinase inhibitor binimetinib in registration for uveal melanoma, and 10 other companies have at least five kinase inhibitors or antibody-based therapies in Phase II testing for the indication. Eli Lilly and Co. markets the antifolate drug Alimta pemetrexed and Reliance Life Sciences markets

VIVACE THERAPEUTICS INC., San Mateo, Calif.

Technology: Hippo-YAP pathway modulators as targeted therapies or immuno-oncology agents

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2015 by Sofie Qiao, Tim Shannon, Edward Hu, Kun-Liang Guan, Bin Liu, Sheng Ding

University collaborators: University of California San Diego, University of California San Francisco

Corporate partners: None

Number of employees: Five

Funds raised: \$40 million

Investors: Canaan Partners, WuXi Healthcare Ventures, Mission Bay Capital, Cenova Capital and Sequoia Capital China

CEO: Sofie Qiao

Patents: None issued

ReliTrexed, an injectable formulation of pemetrexed, for mesothelioma, with at least 30 more compounds in the clinic.

Vivace’s edge over competing therapies may lie in the genetics of the pathway its compounds target. “We think that the application of inhibitors of YAP activation will be driven by tumor genetics more than individual tumor type indications,” Qiao said, adding that the newco is studying the genetic features linked to sensitivity to its compounds.

In July Cancer Research UK and Merck KGaA extended a 2015 deal to develop Hippo-YAP pathway inhibitors in undisclosed cancers.

Vivace’s other YAP-related program aims to activate YAP signaling, and is based on work from co-founder Kun-Liang Guan’s lab at the University of California San Diego that taps LATS1 and LATS2, the pathway kinases responsible for YAP phosphorylation. In a 2016 *Cell* study, Guan’s group showed inhibition of LATS activity enhanced antitumor responses and reduced tumor growth in mouse models of breast cancer,

head and neck cancer and melanoma. Guan is professor of pharmacology at UCSD.

“If you turn on YAP in lines not already addicted to it for survival, they become very immunogenic,” Post said. Vivace’s LATS inhibitor program is in the hit-to-lead stage.

Vivace has filed an undisclosed number of patent applications covering modulation of Hippo-YAP signaling. **■**

COMPANIES AND INSTITUTIONS MENTIONED

Array BioPharma Inc. (NASDAQ:ARRY), Boulder, Colo.

Cancer Research UK, London, U.K.

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

Merck KGaA (Xetra:MRK), Darmstadt, Germany

Reliance Life Sciences, Rabale, India

University of California San Diego, La Jolla, Calif.

Vivace Therapeutics Inc., San Mateo, Calif.

TARGETS

GαQ (GNAQ) - G protein q polypeptide

GNA11 - G protein subunit α 11

LATS1 - Large tumor suppressor homolog 1

LATS2 - LATS large tumor suppressor homolog 2

YAP1 (YAP) - Yes-associated protein 1

REFERENCES

Moroishi, T., et al. “The Hippo pathway kinases LATS1/2 suppress cancer immunity.” *Cell* (2016)

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