BioCentury
REPRINT FROM APRIL 10, 2017

EMERGING COMPANY PROFILE

UP A NOTCH

BY EMILY CUKIER-MEISNER, SENIOR WRITER

By targeting a protein all Notch receptors use to turn on oncogenes, Cellestia Biotech AG's molecules could treat more patients than therapies against individual Notch receptors or ligands, with less toxicity than other pan-Notch inhibitors.

The Notch family of receptors – NOTCH1, 2, 3 and 4 – have been linked to cancer via an array of mutations that either activate individual Notch receptors or ligands, or inactivate Notch repressors. Roughly half of T cell acute lymphoblastic leukemias, gastric cancers and melanomas have excessive Notch signaling.

While the individual receptors and mutations in them may vary from cancer to cancer, all four promote cancer via a common pathway. Namely, gamma secretase cleaves off the intracellular domains of the receptors which then move into the nucleus and induce expression of oncogenes including v-myc myelocytomatosis viral oncogene homolog (MYC; c-Myc) and hairy and enhancer of split (HES).

Chairman Freddy Radtke and CSO Rajwinder Lehal, Cellestia's co-founders, reasoned that preventing the intracellular domains from driving transcription could treat all patients with excessive Notch signaling, regardless of mutation.

In Radtke's academic lab at Ecole Polytechnique Federale de Lausanne (EPFL) the duo developed a cell-based assay to screen for inhibitors of Notch-dependent gene expression.

CEO Michael Bauer said the screens identified several compounds that disrupted interactions between transcriptional machinery and an undisclosed protein that helps direct the machinery to Notch target genes. The molecules stopped production of MYC and HES in the cells.

"We can really target the pathway downstream of the cascade, independent of the reasons for activation," said Bauer.

EPFL granted Cellestia an exclusive, worldwide license to IP covering the molecules, which the company used as starting points for a medicinal chemistry campaign that yielded lead candidate CB-103, an oral pan-Notch inhibitor.

Bauer said Cellestia has unpublished data showing CB-103 decreased tumor growth in a mouse model of triple-negative breast cancer (TNBC) and increased survival in a mouse model of Notch-positive T-ALL.

In 3Q17 the company will start a Phase I/IIa dose-finding study in patients with advanced cancers. A planned extension phase in about half a dozen cancer types positive for Notch activation will help choose indications for future trials.

Bauer acknowledged that decreased Notch signaling has also been associated with some cancers, and said Cellestia will work only in indications where Notch is clearly an oncogenic driver. The company has developed a companion diagnostic by tracking 30 potential biomarkers in the patients in its early stage trials. In addition, it is developing an antibody-based assay that can recognize the activated intracellular domains of all four Notch receptors.

At least four narrower-spectrum Notch inhibitors are in the clinic, including two in Phase II: OncoMed Pharmaceuticals Inc.'s tarextumab (OMP-59R5), a human HuCal mAb against NOTCH2 and NOTCH3, for small cell lung cancer; and

CELLESTIA BIOTECH AG
Basel, Switzerland

Technology: Inhibitors of Notch-induced gene transcription

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2014 by Freddy Radtke, Rajwinder Lehal, Maximilien Murone, Michael Bauer, Dirk Weber, Roger Meier, Ralf Rosenow

University collaborators: Ecole Polytechnique Federale de Lausanne, Vall d'Hebron Research Institute

Corporate partners: Undisclosed

Number of employees: 6

Funds raised: CHF8 million ($8 million)

Investors: PPF Group, private individuals

CEO: Michael Bauer

Patents: 1 covering Notch signaling inhibitors to treat cancer

demcizumab (OMP-21M18), a humanized IgG2 mAb against the Notch ligand delta-like 4 (DLL4), for multiple cancers. DLL4 binds to all four receptors but is only one of at least five ligands that activate the pathway.

OncoMed co-CSO and SVP of Cancer Biology Tim Hoey told BioCentury he thinks mAbs against upstream components of the Notch pathway would block activity more potently and more selectively than a small molecule against a transcriptional regulator could. But Bauer said Cellestia's preclinical work showed CB-103 has adequate selectivity and potency.

Eli Lilly and Co. is going for pan-Notch inhibition with LY3039478, a gamma secretase inhibitor in Phase II testing for T-ALL and T cell lymphoblastic leukemia. Although LY3039478 could treat patients with a variety of mutations, Bauer said it won't work on rare, constitutively active forms of Notch that don't require cleavage by gamma secretase.

Gamma secretase inhibitors also cause GI toxicity, said Bauer, a problem he thinks is less likely with CB-103 because its target is more specific to the Notch pathway. If GI toxicity did arise, he said the company could get around it with intermittent dosing, taking advantage of CB-103's short half-life.

"We believe it's a matter of the right target, the right PK, and managing exposure in an intelligent way, which we can do with a relatively short-lived compound," he said.

Lilly declined to comment.

Bauer said Cellestia has enough funding to begin the Phase I/IIa trial and plans to raise a CHF10 million ($10 million) series A round to complete it, after which it will seek a partner. bc

COMPANIES AND INSTITUTIONS MENTIONED

Cellestia Biotech AG, Basel, Switzerland
Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
OncoMed Pharmaceuticals Inc. (NASDAQ:OMED), Redwood City, Calif.

REFERENCES

Leviten, M. "Notching up differences." *BioCentury Innovations* (2016)
McCallister, E. "OncoMed's multimodal insight." *BioCentury* (2009)

BIOCENTURY INC.

NEWSROOM
pressreleases@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589