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Innovations
FROM IDEA TO IND

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PRODUCT R&D

A SOLID MOVE

By Mark Zipkin, Staff Writer

Following its IPO in March, Cantargia AB is shifting the focus of its lead program from cancers of the blood to solid tumors. After finding its anti-IL-1RAP mAb affects the tumor microenvironment as well as acting directly on tumor cells, the company realized the compound could have greater potential in pancreatic and lung cancers than its originally planned indication of chronic myelogenous leukemia (CML).

The Lund University spinout built its lead compound, CAN04, based on research showing IL-1RAP was present at high levels on surfaces of cancer stem cells in CML, but not on healthy bone marrow cells. This week, the company presented data at a meeting sponsored by brokerage Sedermera Fondkommission showing IL-1RAP is expressed in about 80% of non-small cell lung cancer (NSCLC) cells and 70% of pancreatic cancer cells, which is comparable to its expression levels in acute myelogenous leukemia (AML).

Cantargia was founded in 2010 by Lund researchers Thoas Fioretos, Marcus Järås and Kjell Sjöström with the help of Lund University Bioscience AB, the university's biotech commercialization arm. Fioretos and Järås are professors in the Department of Clinical Genetics at Lund. Sjöström is director at Innovagen AB.

The company's original choice to focus on leukemia was based on the finding that IL-1RAP, a signaling subunit of the IL-1 receptor, was present on leukemia stem cells and could be a target for leukemia therapy, said CEO Göran Forsberg.

The team produced a polyclonal antibody against IL-1RAP to induce antibody-dependent cell-mediated cytotoxicity (ADCC) in the stem cells, with the idea that the compound could complement and shorten treatment times for standard of care CML therapies such as Novartis AG's Gleevec imatinib and Tasigna nilotinib, or Bristol-Myers Squibb Co.'s Sprycel dasatinib. While those compounds are effective in the vast majority of CML patients, they involve lifelong daily treatment, and have little potency against the small population of cancer stem cells containing the Philadelphia chromosome.

In September, Cantargia presented data at the Nordic Life Science Days conference showing that CML and metastatic malignant melanoma patients whose tumors had high IL-1RAP expression had lower survival rates than patients whose tumors had low IL-1RAP expression.

In April, an independent group from the Albert Einstein College of Medicine published data in *Blood* showing a similar relationship between IL-1RAP expression and AML outcomes in patients.

However, as the company laid plans for pursuing CML, it found that wasn't the best place to start for two reasons: the medical need is lower, and the indication didn't fully capitalize on the immune defense properties of CAN04 that can act inside solid tumors.

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>
> Göran Forsberg, Cantargia

"Due to the quite long timelines in process development and large-scale production, we still had some time to explore the solid tumors in more detail," Forsberg told BioCentury. "What we have now is an antibody which will have a direct antitumor effect, but it's also an anti-inflammatory agent that could kill the tumor cells and reduce inflammation inside the tumor."

TIME TO RETHINK

Forsberg was brought in as CEO in 2014 to take the company public and move it beyond its consultancy-run mode. The IPO raised it SEK44 million ($5.1 million), allowing it to initiate tox studies and scale-up for clinical trials planned in 2016.

Cantargia signed two deals this year. First, it licensed a mammalian cell line from BioWa Inc., a Kyowa Hakko Kirin Co. Ltd. subsidiary, that produces antibodies with more potent ADCC than those obtained in a standard production system. Next, it signed an agreement with Glycotope GmbH for product development using the BioWa cell line.

In parallel with the two deals, Cantargia's research group explored the activity of CAN04 in a range of other cancer types.

Forsberg said the compound has two activities: it uses ADCC to cause immune-mediated killing of tumor cells, and it blocks IL-1RAP signaling triggered by IL-1, IL-33 and other proteins in the tumor microenvironment.

According to Forsberg, NSCLC and pancreatic cancer showed higher IL-1RAP expression than hematological tumors. That finding, together with the medical need and market size in solid tumors, led the company to change course, he said.

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"Although we still believe that leukemias would be good indications, we're initially switching directions. All our data indicate that lung cancer and pancreatic cancer will be two splendid opportunities to start with," he added.

Cantargia declined to disclose efficacy data for CAN04 in pancreatic cancer and NSCLC, but noted that in toxicological studies, single 5 mg/kg doses of CAN04 produced no symptoms up to one week post-injection, including no changes in any hematological parameters. In its presentation, the company said 5 mg/kg is a therapeutic dose level.

The tox study was performed in an undisclosed animal model, but Forsberg said a species was selected where CAN04's binding affinity for the IL-1RAP protein is similar to its affinity for human IL-1RAP.

Forsberg said the company's next plans are to complete additional preclinical and larger-scale toxicology studies, with the goal of initiating a Phase I/IIa trial in the solid tumors in late 2016.

Cantargia also has promising data in colon and breast cancers.

"Since the IL-1 system is also involved in autoimmune and inflammatory diseases, if you look further down the line, we could at some point in time probably expand our platform there as well," said Forsberg.

He added that Cantargia isn't giving up on leukemia. A clinical study in AML is planned for 2017 to search for signs of biological activity for CAN04.

Cantargia isn't the only company targeting IL-1RAP in cancer. Cellerant Therapeutics Inc. received an SBIR grant through the National Cancer Institute (NCI) in 2014 to develop CSC012, its anti-IL-1RAP antibody, for AML.

COMPANIES AND INSTITUTIONS MENTIONED

Albert Einstein College of Medicine, New York, N.Y.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Cantargia AB (SSE:CANTA), Lund, Sweden
Cellerant Therapeutics Inc., San Carlos, Calif.
Glycotope GmbH, Berlin, Germany
Innovagen AB, Lund, Sweden
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151), Tokyo, Japan
Lund University, Lund, Sweden
Lund University Bioscience AB, Lund, Sweden
National Cancer Institute (NCI), Bethesda, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland

TARGETS AND COMPOUNDS

IL-1 - Interleukin-1
IL-1RAP - Interleukin-1 receptor accessory protein
IL-33 (NF-HEV) - Interleukin-33

REFERENCES

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EDITORIAL & RESEARCH

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

Editor: C. Simone Fishburn, Ph.D.

Associate Editor: Michael J. Haas

Senior Writers: Lauren Martz; Stephen Parmley, Ph.D.

Staff Writers: Selina Koch, Ph.D.; Mary Romeo; Karen Tkach, Ph.D.; Mark Zipkin

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BioCentury Publications, Inc.
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MAIN OFFICES
PO Box 1246
San Carlos CA 94070-1246
+1 650-595-5333; Fax: +1 650-595-5589

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