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Emerging Company Profile

APIM: Besting the stress defense

By Michael J. Haas
Senior Writer

Chemotherapies and other cancer drugs induce apoptosis by causing genotoxic and other cellular stresses, but the ability of cancer cells to overcome such stress can limit efficacy. By targeting a master regulator of cellular responses to stress, **APIM Therapeutics A/S**'s lead compound could improve the efficacy of approved drugs to treat multiple myeloma and other cancers.

Proliferating cell nuclear antigen (PCNA) plays a key role in the replication of normal cells by interacting with more than 200 proteins that contain the PCNA-interacting peptide (PIP box) motif.

PCNA also is up-regulated in proliferating cancer cells. Its role in cancer was not well understood until researchers from the **Norwegian University of Science and Technology** (NTNU) reported that PCNA interacted with alkylation repair homolog 2 (ALKBH2; ABH2) and several other proteins that did not contain PIP box.

The researchers, led by Marit Otterlei, identified a five-residue motif in ABH2 — dubbed ABH2-interacting peptide motif (APIM) — that interacted with PCNA. The team's database searches identified APIM in more than 200 proteins involved in DNA repair, transcription and cell cycle regulation.

Furthermore, a peptide containing APIM increased HeLa cells' sensitivity to apoptosis induced by DNA alkylating agents compared with cells lacking the peptide. Collectively, the findings led the team to speculate that peptides containing APIM could mediate PCNA's ability to bind to many proteins involved in DNA repair and cell cycle control during genotoxic stress.

Results were published in 2009 in the *Journal of Cell Biology*.

Otterlei is professor of cancer research and molecular medicine at NTNU and founder and CSO of APIM Therapeutics, which was spun out of the university in 2009 to commercialize the findings. The company's lead compound, ATX-101, is an APIM-containing peptide in preclinical development to treat multiple myeloma (MM).

According to CEO Konstantinos Alevizopoulos, APIM has unpublished data showing that in multiple human cancer cell lines, ATX-101 monotherapy increased apoptosis compared with vehicle. The compound also had an additive effect on apoptosis when combined with chemotherapies and targeted therapies. Based on these results, "we think ATX-101 could lower the effective dose of many other cancer drugs and thus reduce their side effects," he said.

APIM chose MM as a lead indication because those cell lines exhibited the greatest sensitivity to ATX-101 alone or in combination with other drugs, includ-

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APIM Therapeutics A/S

Trondheim, Norway
Technology: Peptide-based inhibitors of proliferating cell nuclear antigen (PCNA)
Disease focus: Cancer
Clinical status: Preclinical
Founded: 2009 by Marit Otterlei
University collaborators: Norwegian University of Science and Technology
Corporate partners: NA
Number of employees: 3
Funds raised: €1.7 million ($1.2 million)
Investors: Birk Venture, Ro Invest and Sarsia Seed
CEO: Konstantinos Alevizopoulos
Patents: None issued

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APIM Therapeutics,
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ing Velcade bortezomib, Alevizopoulos said.

Otterlei added that ATX-101 has shown no toxicity in mice, likely because the APIM-binding form of PCNA occurs only in cells that are under stress.

Indeed, she said, ATX-101's apparent lack of toxicity coupled with its ability to improve the therapeutic index of other cancer drugs suggests that the compound could be used in combination with first-line MM therapies.

Last year, APIM Therapeutics raised €1.7 million ($1.2 million) in a seed round of venture financing, which Alevizopoulos expects to last until year end.

The company is optimizing the pharmacokinetic properties of ATX-101 and is looking for international investors to help move the compound into the clinic in MM. The goal is to raise raise enough to complete IND-enabling studies in 18-24 months.

The company plans to seek a pharma partner to help develop ATX-101 in combination with approved drugs to treat non-MM cancers, Alevizopoulos said.

APIM Therapeutics has applied for patents covering APIM-containing compounds and their uses to treat cancer and hyperproliferative disorders. The company also has right of first refusal to additional IP generated by Otterlei's group at NTNU.

Heat shock protein (Hsp) inhibitors are the most advanced class of compounds that block stress responses to treat cancer. There are at least 12 companies with Hsp inhibitors in Phase I through Phase III trials for various cancers.

The **Millennium Pharmaceuticals Inc.** unit of **Takeda Pharmaceutical Co. Ltd.** and **Johnson & Johnson** market Velcade, a small molecule dipeptide boronic acid proteasome inhibitor, to treat MM and mantle cell lymphoma (MCL).

COMPANIES AND INSTITUTIONS MENTIONED

APIM Therapeutics A/S, Trondheim, Norway

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.

Millennium Pharmaceuticals Inc., Cambridge, Mass.

Norwegian University of Science and Technology, Trondheim, Norway

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan