EMERGING COMPANY PROFILE

TARGETED DISRUPTION

BY JENNIFER RHODES, STAFF WRITER

PEP-Therapy S.A.S. is developing fusion peptides for cancer that block specific intracellular protein-protein interactions, which could be safer than broad inhibitors of the same proteins.

The company's fusion peptides comprise an optimized cell-penetrating peptide that shuttles a short interfering peptide into the cell.

The shuttle is a 12-amino-acid peptide derived from an enzyme in a cattle parasite. The biotech modified the peptide with point mutations to prevent degradation by proteases, which in turn improves *in vivo* stability and cellular uptake compared with earlier attempts at developing therapeutic cell-penetrating peptides.

The interfering peptide targets a particular binding site on an enzyme to block a specific protein-protein interaction, while leaving the rest of the target protein's function intact. The binding sites were identified by co-founder Angelita Rebollo and colleagues at the Institut National de la Santé et de la Recherche Médicale (INSERM).

PEP-Therapy's lead program, DPT-PEP1 (DPT-C9h), targets a binding site between protein phosphatase 2 (PPP2CA; PP2A) and caspase-9 (CASP9; MCH6).

In one of its many physiological roles, PPP2CA sequesters CASP9 in a complex that prevents CASP9 from being dephosphorylated. Dephosphorylated CASP9 triggers apoptosis.

According to CEO Antoine Prestat, the PPP2CA/CASP9 complex has a different shape and is more stable in cancer cells than in healthy cells, which helps cancer cells evade apoptosis.

Targeting either of the two enzymes is tricky. PPP2CA is implicated in many essential processes, including cell proliferation and apoptosis, as well as DNA damage repair. And CASP9 is part of a family of closely related cysteine proteases that are expressed in healthy tissues and tumors.

Prestat said DPT-PEP1 does not block the enzymes themselves, but rather causes the PPP2CA/CASP9 complex to become disassociated, allowing CASP9 to be dephosphorylated.

PEP-THERAPY S.A.S.
Evry, France

Technology: Bifunctional fusion peptides comprising an optimized cell-penetrating shuttle and a peptide that blocks a specific protein-protein interaction

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2014 by Antoine Prestat, Didier Decaudin, Fariba Némati and Angelita Rebollo

University collaborators: Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Curie and Pierre and Marie Curie University

Corporate partners: CleveXel Pharma S.A.S.

Number of employees: 5

Funds raised: €1.3 million ($1.4 million)

Investors: Seventure Partners, Bernard Majoie

CEO: Antoine Prestat

Patents: None issued

The company published data in *PLoS One* in 2013 showing that DPT-PEP1 induced CASP9-dependent apoptosis in three cell lines: melanoma, breast cancer and non-small cell lung cancer. In mouse xenograft models, DPT-PEP1 inhibited tumor growth compared with vehicle. Tumor growth was not inhibited in mice receiving either the shuttle alone, or a mutated interfering peptide.

Prestat said DPT-PEP1 appears to be selective for the complex in cancer cells for reasons the company does not yet understand. The *PLoS One* paper includes data showing that the peptide has an apoptotic effect on B cells isolated from chronic lymphocytic leukemia patients, but not on cells isolated from healthy volunteers.

He said the company hypothesizes that the selectivity is due to a difference in proteins that associate with the complex in cancer cells, but PEP-Therapy is still investigating the precise proteins and mechanism.

At least one competitor is developing a PPP2CA inhibitor to treat cancer.

Lixte Biotechnology Holdings Inc.'s LB-100 is in Phase I testing. According to the company's website, animal studies suggest the small molecule PPP2CA inhibitor can be given daily for five days with no limiting toxicity, or intermittently with no observable toxicity.

Other companies targeting PPP2CA are working on activators to restore levels of PPP2CA to normal in cancers where the protein is down-regulated.

PEP-Therapy plans to move DPT-PEP1 into the clinic in 18 months to two years in triple-negative breast and ovarian cancer in combination with chemotherapy, where Prestat said DPT-PEP1 provided an "additive to synergistic effect" in animal models. PEP-Therapy also is developing a companion diagnostic that detects undisclosed genes that Prestat said correlate with responders.

PEP-Therapy also has two other preclinical programs. DPT-PEP2 blocks the interaction of Ras/RAF. DPT-PEP3 blocks the interaction of three proteins in the Hippo signaling pathway.

PEP-Therapy aims to raise €5-€10 million by early 2016; Prestat declined to comment on how much runway the funding would provide.

The company has an exclusive, worldwide license from INSERM to IP covering its cell-penetrating peptide technology, three programs and the DPT-PEP1 diagnostic biomarkers. bc

COMPANIES AND INSTITUTIONS MENTIONED

Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France

Lixte Biotechnology Holdings Inc. (OTCQB:LIXT), East Setauket, N.Y.

PEP-Therapy S.A.S., Evry, France

REFERENCES

Arrouss, I. "Specific targeting of caspase-9/PP2A interaction as potential new anti-cancer therapy." *PLoS One* (2013)