Emerging Company Profile

Piqur: Optimizing dual inhibition

By Tim Fulmer
Senior Writer

Piqur Therapeutics Inc. has developed a dual inhibitor of PI3K and mTOR that it says could treat solid tumors more effectively than dual PI3K/mTOR inhibitors in the clinic because it hits both targets with potencies that are optimized to enhance the overall inhibitory effect on PI3K/mTOR signaling.

Signaling by phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR; FRAP; RAFT1) promotes cell proliferation and survival. Because the PI3K/mTOR pathway is over-activated in cancer, the original rationale behind dual PI3K/mTOR inhibition was straightforward: hit both targets with equal potency and block signaling through the pathway.

However, that approach became less straightforward when researchers discovered that too much mTOR inhibition actually increased signaling through the PI3K pathway. That was because strong mTOR inhibition blocked a negative feedback loop that otherwise dampened PI3K signaling in normal and cancer cells.

Piqur's lead preclinical dual inhibitor, PQR-309, thus was designed to inhibit PI3K with greater potency than mTOR. "That should ensure we inhibit PI3K and mTOR while keeping the negative feedback loop active," CEO, CSO and Head of IP Vladimir Cmiljanovic told BioCentury.

At least five PI3K/mTOR dual inhibitors are in the clinic. The most advanced is **Novartis AG**'s BEZ235, which is in Phase IIb testing to treat cancer. Four other inhibitors are in Phase I testing to treat solid cancers: XL765 from **Exelixis Inc.** and **Sanofi**, GSK2126458 from **GlaxoSmithKline plc**, PF04691502 from **Pfizer Inc.** and PWT33597 from **Pathway Therapeutics Inc.**

Piqur is not yet disclosing any data on PQR-309. Thus, it is unclear how the compound generally compares with other molecules in the class.

Piqur Therapeutics Inc.

Basel, Switzerland
Technology: Small molecule kinase inhibitors
Disease focus: Cancer
Clinical status: Preclinical
Founded: 2011 by Vladimir Cmiljanovic, Matthias Wymann and Bernd Giese
University collaborators: Basel University, Cambridge University, Institute of Cancer Research
Corporate partners: Not disclosed
Number of employees: 10
Funds raised: Not disclosed
Investors: Not disclosed
CEO: Vladimir Cmiljanovic
Patents: Two patent series covering small molecule kinase inhibitors

However, Cmiljanovic was willing to compare PQR-309 with BEZ235. He and his fellow cofounders are familiar with the latter molecule, as they collaborated with Novartis on the preclinical characterization of BEZ235 as researchers at the **University of Basel**.

According to Cmiljanovic, BEZ235's strong mTOR inhibition "leads to loss of the PI3K negative feedback loop. Also, the compound's weak PI3K inhibition makes it likely PI3K can activate mTOR-independent tumor growth pathways."

BEZ235 also has poor solubility compared with PQR-309, Cmiljanovic said.

By designing PQR-309 to avoid BEZ235's issues, he said, "we believe we can generate a more potent inhibitor that will compete with advanced PI3K/mTOR inhibitors like BEZ235 as well as PI3K inhibitors."

At least 12 PI3K inhibitors are in clinical trials to treat solid and hematological cancers as well as inflammatory diseases. Many of these are designed to selectively target one of the four PI3K isoforms — alpha, beta, gamma and delta — which have different tissue distributions *(see BioCentury, Feb. 27)*.

PQR-309 is designed to hit all four PI3K isoforms. "That means we can potentially treat a wider range of cancers and have better efficacy than an isoform-selective inhibitor," said Cmiljanovic.

Piqur has eight other small molecule kinase inhibitors in preclinical development. One of them is PQR-401 a second PI3K/mTOR dual inhibitor. PQR-316 is a PI3K/mTOR/JAK1 inhibitor; while PQR-311 is a PI3Kdelta/mTOR dual inhibitor.

"We use high throughput screens and cellular assays to identify leads. We then generate co-crystal structures of the compounds bound to PI3K isoforms," said Cmiljanovic. Computational modeling guides the optimization.

Roger Williams, professor of molecular biology at **Cambridge University**, carries out the protein X-ray crystallography studies. Marketa Zvelebil, a researcher at the **Institute of Cancer Research**, does the computational modeling.

"Piqur aims to close round A financing in Q312," said Cmiljanovic, who declined to provide details.

COMPANIES AND INSTITUTIONS MENTIONED

Cambridge University, Cambridge, U.K.
Exelixis Inc. (NASDAQ:EXEL), South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Institute of Cancer Research, London, U.K.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pathway Therapeutics Inc., San Francisco, Calif.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Piqur Therapeutics Inc., Basel, Switzerland
Sanofi (Euronet:SAN; NYSE:SNY), Paris, France
University of Basel, Basel, Switzerland