

Emerging Company Profile**Pathway: Function follows PI3K isoform**

By Michael J. Haas
Senior Writer

Many PI3K inhibitors in development cause severe side effects that limit dosing, and most mTOR inhibitors have limited effectiveness because they target only one of the two mTOR complexes involved in cancer cell growth. **Pathway Therapeutics Inc.** thinks its dual PI3K alpha/mTOR inhibitor can treat solid tumors more effectively and safely because it selectively targets a single PI3K isoform and both mTOR complexes.

Signaling by phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR; FRAP; RAFT1) promotes a diverse range of cellular functions, including cell growth, proliferation, survival and metabolism. The two pathways are often dysregulated in cancer cells and are thus common targets, with two mTOR inhibitors on the market and at least 14 PI3K inhibitors in clinical trials for cancer.

Dual inhibition of PI3K and mTOR has been shown to be more effective than inhibiting either protein alone in preclinical tumor models, according to President and CEO Julie Cherrington.

Indeed, at least four companies have PI3K/mTOR inhibitors in Phase I or Phase I/II trials. But Pathway's PWT33597 will be the first PI3K alpha/mTOR inhibitor in the clinic when the company starts a Phase I trial in solid tumors next month. The company thinks the compound will have advantages over competing compounds against the individual targets.

Of the four PI3K isoforms, only PI3K alpha is a key player in the growth of solid tumors, where it is frequently mutated or upregulated. Nevertheless, most PI3K inhibitors in development to treat cancer inhibit all four isoforms because similarities among them has made identifying isoform-specific inhibitors challenging and because the importance of PI3K alpha's role in cancer has become understood only in the last five years or so, according to Cherrington.

She said inhibiting the gamma and delta isoforms in particular can cause myelosuppressive side effects.

Meanwhile, PWT33597 also inhibits both mTOR complexes 1 and 2 (mTORC1 and mTORC2) to turn off a feedback loop that upregulates PI3K when only mTORC1 is inhibited.

Pathway Therapeutics Inc.

San Francisco, Calif.

Technology: Isoform-specific inhibitors of phosphoinositide 3-kinase to treat cancer and inflammatory disease

Disease focus: Cancer, inflammation

Clinical status: Phase I

Founded: 2008 by William Denny and Peter Shepherd

University collaborators: None

Corporate partners: None

Number of employees: 5

Funds raised: \$17 million

Investors: GBS Venture Partners, CM Capital Investments, Breast Cancer Research Trust, Trans-Tasman Commercialization Fund and New Zealand Venture Investment Firm

CEO: Julie Cherrington

Patents: None issued

According to Cherrington, rapamycin analogs — such as the marketed drugs Afinitor everolimus from **Novartis AG** and Torisel temsirolimus from **Pfizer Inc.** — bind the active mTOR site in a manner that inhibits only mTORC1.

“By targeting PI3K alpha, mTORC1 and mTORC2, we hit the cancer pathway at multiple points to make sure we shut it down with greater efficacy than a single-target inhibitor,” she said. “Also, because PWT33597 is such a selective inhibitor, we hope to avoid the dose-limiting liver, lung, and central nervous system toxicities associated with compounds targeting this pathway.”

PWT33597 was specific for PI3K alpha and mTOR in an assay of 442 human kinases and 64 other pharmacological targets, Cherrington said. The company selected the compound as a lead after conducting an SAR study of about 300 dual PI3K alpha/mTOR inhibitors that were generated from a scaffold discovered by the company's cofounders at the **University of Auckland**.

Because Pathway's scaffold binds the active site of mTOR in a different manner than rapamycin analogs, “from the outset we expected that our compounds would inhibit both mTORC1 and mTORC2,”

Cherrington said.

PWT33597 blocked growth and survival in breast, ovarian, brain, colorectal and lung cancer cell lines *in vitro*. In mice bearing brain, breast, colorectal, lung and ovarian xenografts, the compound reduced tumor growth to a greater extent and at lower doses than GDC-0941, a PI3K inhibitor from **Roche's Genentech Inc.** unit that is in Phase I testing for solid tumors.

In its preclinical studies of PWT33597, Pathway has not seen any off-target effects, “but we have seen an expected transient rise in plasma insulin after dosing — a common effect of PI3K, mTOR, and dual PI3K/mTOR inhibitors” that is thought to be target-related, Cherrington said.

The company presented the selectivity, *in vitro* and *in vivo* results at the **American Association for Cancer Research (AACR)** meeting in April.

The company plans to choose a lead indication for PWT33597 after reviewing Phase I data.

“Endometrial, colorectal and breast cancers would be at the top of our list because mutant PI3K alpha occurs in about 30% of those tumor types,” Cherrington said. Tumors driven by the mTOR pathway, such as renal cell carcinoma (RCC), sarcomas, and neuroendocrine tumors also would be strong contenders, she said.

Pathway also has PI3K delta inhibitors in lead optimization to treat hematological malignancies and inflammatory diseases, and irreversible PI3K inhibitors — which the company expects will be selective for PI3K alpha — in lead optimization to treat cancer.

Cherrington said Pathway has sufficient funding for 18 months — long enough to complete the Phase I trial of PWT33597.