PI3K δ inhibition: solid immunotherapy

By Michael J. Haas, Senior Writer

Until now, inhibition of phosphoinositide 3-kinase- δ in cancer has been limited to leukemias and lymphomas because the isoform is only expressed on immune cells. A new finding that links the kinase to T cell responses in a range of solid tumor types could expand use of the inhibitors and launch a new class of immunotherapies.¹

The team behind the study is planning a clinical trial of an undisclosed phosphoinositide 3-kinase- δ (PI3K δ) inhibitor in solid tumors.

PI3K δ is one of four PI3K isoforms that play key roles in cell growth, differentiation and survival. The PI3K α and PI3K β isoforms are expressed in nearly all cell types and have been targeted in solid tumors, whereas the PI3K γ and PI3K δ isoforms are found primarily on immune cells.

Several companies are developing inhibitors of PI3K δ for hematological malignancies, autoimmune diseases and inflammatory

indications in which the isoform is overactive (see Table 1, “A peek at PI3K δ inhibitors”).

In a series of studies over the last decade, the team’s principal investigators, Bart Vanhaesebroeck and Klaus Okkenhaug, studied a mutant, catalytically inactive form of PI3K δ and showed the subtype to be important for the differentiation, expansion and normal function of T and B cells.²⁻⁵

Vanhaesebroeck is a professor of cell signaling at the **University College London Cancer Institute**, and Okkenhaug is group leader in the laboratory of lymphocyte signaling and development at the **Babraham Institute**.

Vanhaesebroeck told *SciBX* that for the new study, he and his colleagues initially thought that because mice with mutant PI3k δ have compromised immune responses, they might be more prone to developing solid cancers than wild-type mice.

However, when the researchers established tumors in mutant PI3k δ mice with cells from breast, lung and other solid tumors, they saw the opposite of what they expected. The mutant mice developed smaller primary tumors and fewer metastases and survived longer than wild-type mice given the same treatment.

In addition, PI-3065—a PI3K δ inhibitor from **Roche’s Genentech Inc.** unit—decreased growth of breast and pancreatic tumors in wild-type mice and increased survival compared with vehicle.

PI-3065 was originally developed by Piramed Ltd., which was acquired by Roche in 2008.

Next, the team investigated the link between PI3K δ inhibition and its effects on the immune system in solid tumors and focused on several T cell populations that have known roles in antitumor immunity.

Table 1. A peek at PI3K δ inhibitors. According to a study in *Nature* by Ali *et al.*, inhibition of phosphoinositide 3-kinase- δ (PI3K δ) or the PI3K catalytic subunit δ -polypeptide (PI3KCD; p110 δ) could treat solid tumors by modulating T cell responses. At least 12 companies are developing PI3K δ -specific inhibitors or dual PI3K γ and PI3K δ inhibitors for hematological malignancies, autoimmune disease and inflammation that could be repurposed to treat solid cancers.

Source: *BCIQ: BioCentury Online Intelligence*

Company	Product	Description	Status
Gilead Sciences Inc. (NASDAQ:GILD)	Idelalisib	Small molecule inhibitor of PI3K δ	In registration for chronic lymphocytic leukemia (CLL) and non-Hodgkin’s lymphoma (NHL)
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)/Infinity Pharmaceuticals Inc. (NASDAQ:INFI)	IPI-145	Oral inhibitor of PI3K γ and PI3K δ	Phase III for CLL; Phase II for NHL, lymphoma, rheumatoid arthritis (RA) and inflammation; Phase I for hematological malignancies and autoimmune diseases
Rhizen Pharmaceuticals S.A./TG Therapeutics Inc. (NASDAQ:TGTX)	TGR-1202	PI3K δ inhibitor	Phase I/II for CLL, B cell lymphoma and hematological malignancies
Amgen Inc. (NASDAQ:AMGN)	AMG 319	Small molecule inhibitor of PI3K δ	Phase I for hematological malignancies
Incyte Corp. (NASDAQ:INCY)	INCB40093	PI3K δ inhibitor	Phase I for B cell lymphoma
Gilead Sciences	GS-9820	PI3K δ inhibitor	Phase I for lymphoma
Rhizen Pharmaceuticals	RP6530	Dual PI3K γ and PI3K δ inhibitor	Phase I for hematological malignancies; preclinical for B cell lymphoma and T cell lymphoma
	RP6503	Dual PI3K γ and PI3K δ inhibitor	Preclinical for asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and inflammation
Exelixis Inc. (NASDAQ:EXEL)/Merck & Co. Inc. (NYSE:MRK)	XL499	Selective inhibitor of PI3K δ	Preclinical for cancer and inflammation
Pathway Therapeutics Inc./MEI Pharma Inc. (NASDAQ:MEIP)	PWT143	PI3K δ inhibitor	Preclinical for cancer
Xcovery Holding Co. LLC	X-339	Selective inhibitor of the p110 δ isoform of PI3K	Preclinical for CLL

In mice, mutant PI3K δ moderately reduced the activity of tumor antigen-specific CD8⁺ T cells but inactivated T_{reg} cells that ordinarily eliminate CD8⁺ T cells. Because PI3K δ deficiency had a larger impact on T_{reg} cells than on the CD8⁺ T cells, the net result was a gain in antitumor immunity.

Furthermore, in mice with pancreatic tumors, PI-3065 decreased the number of T_{reg} cells in draining lymph nodes and increased the number of CD8⁺ T cells in primary tumors and in draining lymph nodes.

The team concluded that PI3K δ suppression enhanced antitumor immune responses in the mice.

The team included researchers from the **Medical Research Council's** Harwell campus, **Queen Mary University of London** and Roche's Genentech and Piramed units who assisted with the PI-3065 experiments.

Results were published in *Nature*.

Taken together, the team's findings suggest that PI3K δ inhibitors could treat solid tumors by "tipping the immune system balance in favor of the tumor-targeting CD8⁺ T cells," Vanhaesebroeck told *SciBX*.

The team is also elucidating the mechanism by which PI3K δ deficiency deactivates T_{reg} cells in the cancer models and has a manuscript under review showing that PI3K δ is expressed in some solid tumors, in which it appears to play a role in tumor cell invasion.

Swaroop Vakkalanka, president of **Rhizen Pharmaceuticals S.A.**, agreed that the findings support the potential of PI3K δ inhibitors to treat solid tumors and said that the *Nature* report begins to shed light on precisely how PI3K δ inhibition exerts its therapeutic effects in those cancers.

He added that his company has unpublished preclinical data showing the efficacy of a dual PI3K γ and PI3K δ inhibitor in solid tumors. Rhizen will decide whether to develop this compound and its PI3K δ -specific inhibitor for solid tumors after conducting additional preclinical studies, he told *SciBX*.

Delivering delta inhibitors

According to Vanhaesebroeck, PI3K δ inhibitors could be used as immunotherapies in combination with other cancer therapies—including surgery and radiation—or even as adjuvants to cancer vaccines.

"We know from clinical trial data that PI3K δ inhibitors are safe and well tolerated by cancer patients, some of whom have received the inhibitors for up to three years," he said. "Stimulating the immune system with something that we already know is safe will open a lot of doors for treating solid tumors."

Lori Friedman, senior director of translational oncology at Genentech and coauthor of the *Nature* study, agreed. But to identify which patients might benefit from PI3K δ inhibitor therapy, she said that "clinical researchers will need to analyze a variety of solid tumor types to understand which ones rely on T_{reg} cells for evading immune responses."

In addition, they will need to investigate how PI3K δ inhibition affects the balance of T_{reg} and CD8⁺ T cell responses in patients, she said.

Vakkalanka added that using PI3K δ inhibitors in combination with other cancer therapies could have additive or synergistic effects that lower the effective doses and thereby provide an added margin of safety for each therapy.

However, he also wanted to see preclinical and clinical studies

combining a PI3K δ inhibitor with immunotherapies that enhance T cell activity against cancer, such as antibodies against programmed cell death 1 (PDCD1; PD-1; CD279). "A PI3K δ inhibitor could support the effectiveness of those therapies in treating cancer by inactivating T_{reg} cells and exerting a broad anti-inflammatory effect," he said.

Because activating mutations in PI3K α frequently occur in solid tumors, the *Nature* findings also point to the possibility that inhibiting both PI3K α and PI3K δ could have therapeutic advantages over inhibiting only PI3K δ , Friedman said.

Indeed, Genentech is interested in determining whether its small molecule PI3K inhibitor pictilisib (GDC-0941; RG7321) has an immunomodulatory effect via PI3K δ inhibition in patients with solid tumors, in addition to having a direct effect on tumor growth via PI3K α inhibition, Friedman told *SciBX*.

Pictilisib is in Phase II testing to treat breast cancer and non-small lung cell cancer (NSCLC). The compound inhibits all four PI3K isoforms with nanomolar potency and is more potent against the PI3K α and PI3K δ isoforms.⁶

However, Vakkalanka said that inhibiting both PI3K α and PI3K δ would not be desirable because the safety profiles of pan-PI3K inhibitors are not as good as those of isoform-specific inhibitors. Thus, he cautioned that finding inhibitors specific for the PI3K δ isoform would be important for retaining a good safety profile.

Vanhaesebroeck agreed. "Immune cells express the α isoform as well as the δ isoform, and some literature studies suggest that inhibiting both isoforms severely compromises the function of immune cells," he said. This means that "hitting too many PI3K isoforms might override the immunotherapeutic effects" of inhibiting PI3K δ .

Vanhaesebroeck said that the team is planning a clinical trial of an undisclosed PI3K δ inhibitor to treat an undisclosed solid tumor type. "We want to look for early evidence that PI3K δ inhibition has an immunomodulatory effect on solid tumors," he told *SciBX*.

The findings are not patented or licensed, he said.

Genentech declined to disclose the development status of PI-3065.

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COMPANIES AND INSTITUTIONS MENTIONED

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Genentech Inc., South San Francisco, Calif.
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