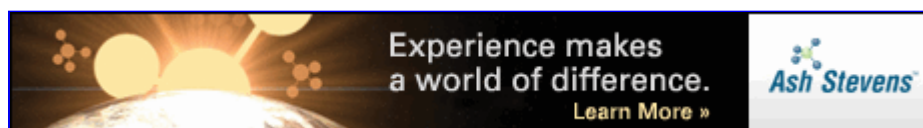


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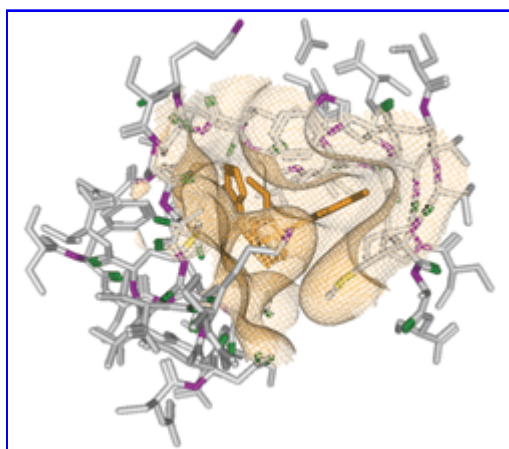
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PI3K At The Clinical Crossroads

After a frenzy to develop better and more selective PI3K inhibitors, companies now must figure out how to use them in cancer patients

[Lisa M. Jarvis](#)



Intellikine [View Enlarged Image](#)

TARGETED ATTACK A PI3K inhibitor (gold) is shown docked to PI3Kδ.

PI3 kinases are obvious targets for researchers developing cancer drugs. Formally known as phosphatidylinositol-3 kinases, the enzymes are involved in a laundry list of functions that contribute to the ability of cells to thrive. By adding a phosphate to signaling molecules, they set off a chain reaction that can lead to protein synthesis, cell survival, cell migration, and blood vessel growth. Their activity is so pervasive that a mutation in one enzyme isoform is present in a wide range of cancers. Drug companies are understandably eager to figure out how to inhibit PI3 kinases.

“Nature is basically painting a big neon sign saying ‘Inhibit Here,’ ” says Troy Wilson, chief executive officer of

[Intellikine](#), a La Jolla, Calif.-based biotech firm focused on developing drugs targeting the PI3K pathway. “There aren’t a lot of oncogenic kinase mutations out there. This may be the last one found that’s implicated in a broad array of tumors.”

But as is often the case in drug discovery, the PI3K story is more complicated than it once seemed. Chemists have spent years developing different PI3K inhibitors that vary in specificity. The broadest ones block the PI3K family of lipid kinases as well as another enzyme in its pathway called mTOR. Other compounds knock down just the PI3K family, and still others selectively inhibit only one of four key isoforms of the enzyme.

The idea is tantalizing: Knock down the target and stop cancer in its tracks. Yet early studies of these compounds in humans suggest that inhibiting PI3K typically has limited therapeutic effect.

PI3K inhibitors, it turns out, work best with other compounds. The challenge for industry and academic researchers in the coming years will be to figure out which medicines they should be paired with to maximize their impact. Clinical trials testing the effect of combining PI3K inhibitors with other drugs are already under way. The task of winnowing out the right drugs for the right patients is complex, but companies are confident that compounds blocking this pathway will one day play a critical role in cancer treatment.

The PI3K signaling pathway is one of the most important in cancer, notes Juan Luengo, director and head of chemistry for cancer metabolism and oncology R&D at [GlaxoSmithKline](#). It’s therefore no surprise that big pharma and biotechs alike are racing to develop drugs that target it. Indeed, the drug development landscape is becoming increasingly crowded: Less than two years ago, 10 PI3K inhibitors were in early clinical trials; today, some 18 compounds are in the clinic and at least two more are expected to enter human studies before the end of the year.

Deal-making around PI3K has also been robust. One of the earlier deals came in 2008, when Roche paid \$160 million for Piramed, a small, U.K.-based biotech firm that was developing PI3K inhibitors in partnership with Roche’s [Genentech](#) affiliate. A year later, Exelixis scored \$140 million-plus research funding when [Sanofi-Aventis](#) licensed its dual mTOR/PI3K inhibitor XL765 and pan-PI3K inhibitor XL147. In February, Gilead Sciences said it would acquire Calistoga Pharmaceuticals for \$375 million, with the promise of \$225 million in milestones as its lead isoform-selective PI3K inhibitor winds toward the market.

“Nature is basically painting a big neon sign saying ‘Inhibit Here.’ ”

Yet this flurry of interest around PI3K belies long-standing knowledge of the importance of the target. It’s been more than 25 years since cell biologist Lewis C. Cantley discovered the kinase and more than 15 years since the first compounds to block PI3K—Eli Lilly & Co.’s LY294002 and the natural product wortmannin—were reported.

Interest in the target rapidly followed. Lilly was reportedly so inundated with requests for samples of LY294002 after disclosing the structure in 1994 that it turned it over to Sigma-Aldrich to be sold as a research tool. Over the years, the compound became a critical starting point for research into the pathway, garnering references in more than 9,000 journal articles, according to Chemical Abstracts Service.

But LY294002 and wortmannin turned out to be less than ideal starting points for investigating the PI3K signaling pathway. The problem, researchers say, was that both compounds are “dirty.” Sure, they knock out all the isoforms of PI3K, but they also hit myriad other targets.

Absent good research tools and encouraged by the approval of the mTOR inhibitor rapamycin, companies for several years turned their sights to developing compounds that block mTOR, a protein downstream of PI3K in the cell signaling pathway. Later, efforts broadened to compounds inhibiting AKT, yet another player in the PI3K network.

By the early 2000s, several factors coincided to advance development of drugs against PI3K. It had become clear that the first generation of compounds to block mTOR had serious limitations, not the least of which was that cancer cells quickly found a feedback loop to PI3K when the mTOR pathway was shut down.

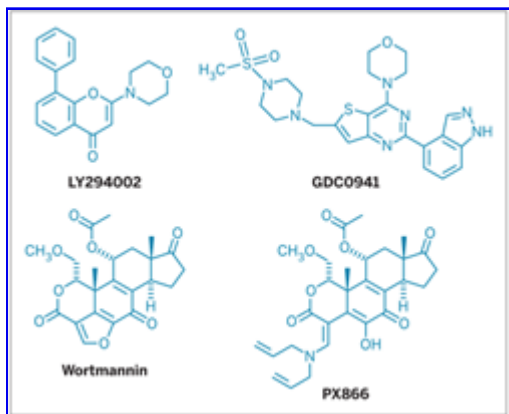
“The big discovery was in 2004, when activating mutations in a catalytic subunit of PI3K α were identified,” says Alan Olivero, associate director of discovery chemistry at Genentech. These mutations were soon understood to be some of the most common in cancer.

The first generations of PI3K inhibitors, now starting to enter midphase clinical trials, knock out both the PI3K family of enzymes and mTOR. Companies with dual mTOR/PI3K inhibitors in the clinic read like a who’s who of big

pharma: [Novartis](#), Genentech, [Pfizer](#), GlaxoSmithKline, Bayer, and Sanofi-Aventis.

[Semafore Pharmaceuticals](#), a tiny Indianapolis-based biotech, was one of the pioneer companies to develop a dual mTOR/PI3K inhibitor. Although many considered the Lilly compound to be too promiscuous and insufficiently potent to be effective, Semafore scientists saw value in its broad activity. It developed a prodrug of LY294002, called SF1126, that delivers the active molecule to solid tumors.

Semafore has completed Phase I studies of the prodrug, which can be administered at higher concentrations than LY294002 without toxicity problems, says Joseph Garlich, the firm's cofounder and chief scientific officer.



[View Enlarged Image](#)

But at big pharma companies, the dual activity of the first generation of compounds wasn't entirely deliberate. Research efforts were hampered by limited knowledge of the pathways at the time, the lack of high-quality chemical probes, and less than ideal assays for lipid kinases, explains Carlos Garcia-Echeverria, global head of oncology medicinal chemistry and pharmacology at Sanofi-Aventis. "Originally we thought the compounds we were developing would be exclusively active against PI3K," Garcia-Echeverria says. "Only retrospectively did we find out they were active against mTOR."

It turns out that hitting both targets shouldn't have been a surprise. "The kinase domains of the two proteins are very similar, so it's reasonable to expect that chemical matter that's active against PI3K would also be active in mTOR," says Robert T. Abraham, chief scientific officer of Pfizer's oncology research unit. "And we certainly uncovered chemical matter that hit both enzymes equally well."

Thanks to a lot of elbow grease by medicinal chemists, the dual inhibitors coming out of the early programs overcame the problems of the Lilly compound and wortmannin. Aided by improved assays and the first crystal structure of a PI3K—the γ -isoform, which is similar enough to its family members to enable the design of compounds that block the whole class—companies were able to dramatically improve the potency of mTOR/PI3K inhibitors and lower their toxicity.

"That's a distinction," GSK's Luengo says. "Our compounds have picomolar activity," which is six orders of magnitude more potent than the Lilly compound.

Although most of the first-generation compounds are less selective than anticipated, the mTOR/PI3K activity could turn out to be an asset, Garcia-Echeverria explains. "One of the current working hypotheses is that compounds that are able to inhibit two components of the same pathway will be less prone to resistant mutations," he says.

Indeed, the beauty of the mTOR/PI3K inhibitors is that they are potent and they deprive cancerous cells of the feedback loop that limited the efficacy of earlier mTOR inhibitors, Pfizer's Abraham says. "We anticipate these compounds will have a more dramatic effect on tumors" than the rapamycin analogs had, he adds.

Although they aren't going to be "the magic bullet," they will be a good part of the therapeutic palette.

Although blocking both mTOR and PI3K makes sense biologically, some researchers question whether it's possible to knock out both targets hard enough to treat cancer and also avoid the kind of toxicity that can shut down a program. "It's not clear yet," says Scott R. Peterson, vice president of R&D at [Oncothyreon](#).

Peterson and his colleagues at Oncothyreon believe those potency and safety concerns can be addressed with

compounds that block only members of the PI3K family of enzymes, leaving mTOR alone. Other companies working on this approach include Novartis, Genentech, and Sanofi-Aventis.

Oncothyreon's lead compound, PX886, is most selective for the α - and β -isoforms of PI3K. Oncothyreon's science has its origins in the labs of University of Pittsburgh synthetic chemist Peter Wipf, who discovered wortmannin's weakness: It doesn't stay in circulation very long because of the chemical reactivity of its C20 position. By modifying the ring at that position, chemists created wortmannin derivatives that were more stable, while retaining their potency as PI3K inhibitors.

Oncothyreon chemists made more than 90 derivatives of the compound in the search for one that would stay in circulation, overcome the liver toxicity associated with wortmannin, and still knock down PI3K's α - and β -isoforms. "PX866 rose to the top," Peterson says. "It's much more stable than wortmannin but maintains high potency against the target."

The compound is being tested in combination with other therapies in two Phase I/II trials, including a study of its effectiveness with ImClone Systems' Erbitux in treating colon cancer. Oncothyreon also expects to start a Phase II trial testing the drug on its own as a treatment for aggressive brain tumors and prostate cancer.

Genentech's pan-PI3K inhibitor, GDC0941, originated at Piramed. Following the creation of a partnership in 2005, the Piramed project team set out to improve upon an early thieno[3,2-*d*] pyrimidine derivative, which had strong activity against PI3K α but that lacked the right pharmacokinetic properties to make a good drug.

After making a series of compounds that retain the morpholino group, believed to be responsible for activity against PI3K α , chemists came up with an indazole derivative that had the right mix of potency, bioavailability, and half-life to affect the entire PI3K family. "It was one of the first really selective PI3 kinase inhibitors with good pharmacokinetic properties out there and a great opportunity for our biologists to start testing hypotheses about which patients it should work in," Olivero says.

The compound, GDC0941, is now in Phase I trials testing the safety of combining it with chemotherapeutics and other targeted therapies in cancers including breast, lung, and non-Hodgkin's lymphoma.

The Oncothyreon and Genentech drugs inhibit most members of the PI3K family, but researchers have more recently become interested in compounds that block a single isoform of PI3K. The argument for this highly targeted approach is that such compounds will be better equipped to work in combination with other therapies. "You want to get maximum efficacy hitting that enzyme, while minimizing off-target activity in order to increase your chances of success," Intellikine's Wilson says.

RUSH TO CLINIC
Many big pharma and biotech firms have PI3K inhibitors in clinical trials

	DRUG	DEVELOPMENT PHASE	MECHANISM
Bayer	BAY806946	Phase I	Dual mTOR/PI3K
Exelixis/Sanofi	XL765	Phase I	Dual mTOR/PI3K
Genentech/Roche	GDC0980	Phase I	Dual mTOR/PI3K
GlaxoSmithKline	GSK2126458	Phase I	Dual mTOR/PI3K
Novartis	BEZ235	Phase I/II	Dual mTOR/PI3K
Novartis	BGT226	Phase I/II	Dual mTOR/PI3K
Pfizer	PFO4691502	Phase I	Dual mTOR/PI3K
Pfizer	PKI587	Phase I	Dual mTOR/PI3K
Semafore	SF1126	Phase I	Dual mTOR/PI3K
Exelixis/Sanofi	XL147	Phase I/II	PI3K
Genentech/Roche	GDC0941	Phase I	PI3K
Novartis	BKM120	Phase I/II	PI3K
Oncothyreon	PX866	Phase I/II	PI3K
Zenyaku Kogyo	ZSTK474	Phase I	PI3K
Novartis	BYL719	Phase I	PI3K α
Amgen	AMG319	Phase I	PI3K δ
Calistoga Pharma	CAL101	Phase I/II	PI3K δ
Genentech/Roche	GDC0032	Phase I	PI3K β

a Mechanism not yet disclosed. SOURCES: Semafore, ClinicalTrials.gov

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Although companies have been working on the approach for several years, new positive data for Calistoga's δ -isoform inhibitor has generated excitement that the highly targeted drugs could be effective in certain cancers.

Calistoga chose to focus on PI3K δ because, unlike the more prevalent α - and β -isoforms, it is only expressed in white blood cells. Since the δ -isoform plays a role in modifying lymphocyte function, the company was initially focused on finding drugs that might have an impact on inflammatory diseases. Then Calistoga scientists considered that the compounds might also be useful in blood cancers, which in essence are “inflammation gone amok,” says Langdon L. Miller, the firm’s vice president of R&D.

In December, Calistoga reported data from two Phase I trials testing its lead compound, CAL101, as both a single agent and in combination with two already approved therapies, Treanda and Rituxan, in patients with chronic lymphocytic leukemia. In the single-agent trial, patients who didn’t respond to at least five other medicines all saw their tumors shrink. The majority also saw a reduction in lymph node swelling of more than 50%.

“Our preliminary data suggest that diseases with the most inflammatory characteristics are the ones that respond best to treatment,” Miller says. “In some ways, these are the patients that on conventional therapy would do the worst.”

Calistoga’s success in the clinic, not to mention its big-ticket acquisition by Gilead, has bolstered other small companies that are developing isoform-selective compounds.

Intellikine was a latecomer to the PI3K field, but it has moved quickly from concept to clinic. The biotech was formed in late 2007 out of technology developed in Kevan M. Shokat’s labs at the University of California, San Francisco. Shokat had found a way to make isoform-selective inhibitors of PI3K and was using them as tools to better understand the role of individual isoforms in different cell types.

Using a set of molecules discovered in Shokat’s lab as a starting point, Intellikine scientists, along with researchers at its Shanghai-based partner Chemikine, made analog after analog in search of compounds that selectively block PI3K δ . By screening with in vivo assays and using crystal structure information, the company ended up with an array of molecules active against multiple isoforms of PI3K. “The beauty is that by screening for compounds that block PI3K δ , by definition you’re going to find compounds that hit other isoforms,” Wilson says.

Later this year, Wilson says, the company will put two isoform-selective compounds into Phase I studies: INK1117, a PI3K α -selective inhibitor, and IPI-145, a PI3K δ/γ dual-selective inhibitor being developed in collaboration with Infinity Pharmaceuticals.

DOUBLE TROUBLE	
Several clinical trials ongoing or planned combine PI3K inhibitors with MEK inhibitors	
PI3K INHIBITOR	MEK INHIBITOR
Genentech GDC0941	+ Genentech GDC0973
GSK GSK2126458	+ GSK GSK1120212
Merck MK-2206	+ AstraZeneca AZD6244
Novartis BKM120	+ GSK GSK1120212
Sanofi-Aventis SAR245408	+ Merck Serono MSC1936369B
Sanofi-Aventis SAR245409	+ Merck Serono MSC1936369B

SOURCES: Companies, ClinicalTrials.gov

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Meanwhile, Novartis has an α -isoform-selective inhibitor in Phase I trials, and Amgen recently started a Phase I trial of its γ -selective inhibitor, AMG319. Other compounds are making progress toward the clinic: Avila Therapeutics last week reported preclinical data on its α -selective inhibitor.

While companies argue the pros and cons of broad versus selective PI3K inhibitors, Genentech sees merit in having an array of therapeutic options. “There are going to be aggressive diseases where you need to clamp down on the pathway very hard and quickly, and other indications where you’ll want a more selective and safe type of inhibitor,” Olivero says.

For example, during the development of GDC0941, a pan-PI3K inhibitor, Genentech and Piramed started work on what would become GDC0980, a dual mTOR/PI3K inhibitor meant to complement the activity of GDC0941. Genentech recently put another PI3K inhibitor, GDC0032, into Phase I trials and is advancing a variety of other inhibitors, Olivero says.

The multiple options are necessary, drug companies say, because so much work remains before researchers

understand how best to apply these new drugs. Years ago, the assumption was that a PI3K inhibitor on its own could produce cell death. And indeed, apoptosis has been observed in laboratory studies of these drugs. But it has become clear that a PI3K inhibitor used on its own is in most cases only keeping tumors from growing, not killing them.

PI3K mutations are acknowledged as being present in most cancers, says [Bart Vanhaesebroeck](#), head of the Centre for Cell Signaling at Barts Cancer Institute in London. “The question now is, what can you expect if you interfere in it? Expectations [for these drugs] have been very high, and in my opinion a little bit too high.”

[Jeffrey A. Engelman](#), director of the Center for Thoracic Cancers at Massachusetts General Hospital, also cautions against too much optimism. “We suspect these drugs aren’t going to be an incredibly effective therapy as a single agent in many cancer types,” he says.

The problem is that PI3K is just one part of a complex signaling network. Blocking one node of that network is rarely effective, as cancer cells are annoyingly clever at finding alternative routes.

The general consensus is these drugs will most often need to be used in combination with some other agent, whether it’s chemotherapy or a second targeted therapy. Having a broad tool kit of PI3K inhibitors from which to choose should help clinicians find the best combination for each patient’s cancer.

But the panoply of options is a double-edged sword. The good news is that the wide range of compounds is an important tool for investigating the biology of disease in the lab and can help inform choices in the clinic. “We have virtually every flavor of selective PI3 kinase inhibitor to work with,” Genentech’s Olivero says. “We’ve been able to ask a lot of very key questions about this pathway.”

But picking apart which cell signaling pathways are turned on in specific cancers to determine drug combinations is a daunting task, Engelman notes. Mapping out the right therapy involves selecting a companion drug and then figuring out whether a single-isoform PI3K inhibitor, a pan-PI3K inhibitor, or a dual mTOR/PI3K inhibitor would work best. Then clinicians must tackle the not-so-trivial task of determining the right way to administer the drug cocktail without causing toxicity.

“I think it will be important that careful laboratory studies are done to move these combinations into the clinic and that we are quick to learn from our clinical experiences to inform future studies,” Engelman says.

An understanding of certain mutations in the PI3K pathway has given researchers some early clues about the best drug combinations and about which patient populations will best respond. One of the more compelling theories is that PI3K inhibitors will work well in combination with drugs that block another cell signaling pathway called KRas/MAPK.

“KRas mutations are associated with many of the deadliest cancers,” including colorectal and pancreatic, Pfizer’s Abraham says. Yet they are incredibly resistant to conventional chemotherapy, and based on preclinical studies of the mutations, are expected to be resistant to the new batch of mTOR/PI3K inhibitors as well, he adds. The working hypothesis is that knocking out two of the major drivers of cancer—the KRas and PI3K pathways—could have a significant effect on the most recalcitrant tumors.

The trick is to find a combination of compounds that knocks down cancer cells without being too toxic to normal cells. Companies already have begun trials testing the combination of PI3K inhibitors with compounds that block MEK, one player in the KRas/MAPK pathway. Both GSK and Genentech have launched Phase I studies testing their pan-PI3K inhibitors with their lead MEK inhibitors.

But combining two agents that have yet to be approved—so far, no MEK inhibitor has reached the market—is a complicated endeavor. “It is complex when you’re dose-escalating different drugs that are still early in the clinical development,” Genentech’s Olivero acknowledges. “We have to do it very cautiously, dosing up one and then the next in a stepwise action.” Genentech last week provided evidence that the cautious approach is working: the company said data from its Phase I study showed the combination of its MEK and PI3K inhibitors is safe enough to move forward into further studies.

As Phase I trials of Genentech’s GDC0980 and GDC0941 wrap up, a series of Phase Ib trials is being rolled out to test combining them with chemotherapy, other targeted agents, and drug candidates from the firm’s pipeline. “Driven by the science, we’ve aggressively started combining our inhibitors with a variety of different agents,” Olivero says.

With so much attention focused on combination studies, it's critical for biotech firms that lack pipeline breadth to find partners. Intellikine has some 50 collaborations ongoing to help determine relevant patient populations for its compounds. "We're collaborating with academic investigators as well as scientists at other companies who have hypotheses about their patient population and how best to treat it," Wilson says.

Even big pharma companies have turned to their competitors to enable combination studies. AstraZeneca and Merck & Co. were the first to partner. They tested a Merck compound blocking AKT, a member of the PI3K pathway, in combination with AstraZeneca's MEK inhibitor. Sanofi is working with Merck Serono, and Merck and GSK have teamed for similar studies.

Despite the uncertainty around how to best use these new compounds, scientists are confident that PI3K inhibitors will eventually be important in the treatment of cancer. Although they aren't going to be "the magic bullet," they will be a good part of the therapeutic palette, Barts Cancer Institute's Vanhaesebroeck says. "We will just have to be smart about how we use them."

"My feeling is that PI3 kinase inhibitors will be a very important part of targeted therapy moving forward," Engelman adds. "This pathway is very important for the survival of cancer cells, but we're still learning how to use these drugs appropriately."

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