

It's Apples Versus Oranges in the PI3 Kinase Race

Early bets placed on PI3K pan-selective inhibitors may pay off, but smart money lately has been focused on isoform-selective inhibition of this signaling pathway implicated in cancer, inflammation, and autoimmune disease.

Someone seeking a clinical space that offers a great deal of activity and anticipation, and where the major developments and deal-making remain around the corner, would have to look no further than the phosphoinositide-3 kinase (PI3 kinase) area.

The subject of two major pharma/biotech alliances in the past year, PI3 kinase drug development in several therapeutic areas is ongoing at several Big Pharma companies along with a host of biotechs. The reason for the enthusiasm becomes clear quickly—PI3 kinases are a family of intracellular signal transducer enzymes that have been implicated in diseases ranging from cancer to inflammatory and autoimmune disorders.

Roughly 90% of a cell's survival signals travel through the PI3K-PTEN (phosphatase and tensin homolog, a tumor-suppressor gene) "pinch point" before reaching the nucleus. Cancer drugs aimed at growth factor receptors have had less impact than hoped for because tumor cells whose access to one receptor is cut off by a drug often are able to receive signaling cascades key to cell growth and division via another receptor—but that's a much harder process if the PI3K-PTEN pinch-point is closed off.

"It's the hot pathway and the hot target in oncology R&D right now," **Exelixis Inc.** president of R&D Michael Morrissey, PhD, tells *START-UP*.

Morrissey knows of what he speaks. In May Exelixis signed a \$140 million up-front worldwide development and commercialization deal with **Sanofi-Aventis** centered around two early-stage PI3K compounds. (See "Ahead Of ASCO, Exelixis Inks Lucrative Deal With Sanofi For Its PI3 Kinase Inhibitors," *The Pink Sheet DAILY*, May 28, 2009.) Biobucks connected to the deal could reach \$1 billion, along with double-digit royalties on any products reaching the market.

"MET was there four or five years ago and PI3K is there right now," Morrissey continues, referring to the oncology target mesenchymal epithelial transition factor. "I think every major pharma has a program, has an interest in the space. A lot of biotechs do too."

A major distinction within PI3K development, however, has developed between pan-selective inhibitors and isoform-selective inhibitors of the target; the latter compounds inhibit the alpha, beta, delta, or gamma isoforms of PI3 kinase, or multiples of them, while leaving the other isoforms undisturbed. By contrast, pan-selective PI3K inhibitors hit multiple points in the pathway, sometimes inhibiting other lipid and protein kinases.

Abingworth partner Ken Haas notes that each approach offers its own qualities and drawbacks.

People are working on different things in different indications, so there's not as much head-to-head (competition) right now among the small companies," he says. "Everyone has a slightly different compound moving against a slightly different indication...a lot of it is apples and oranges in terms of comparison. Some of it may be different types of apples, maybe a Fuji versus a MacIntosh, but there's still enough different tastes among pharma that they're not really going head-to-head."

Most earlier programs, like Exelixis' XL 765 and XL 147, both of which have reached Phase II in oncology, and **Semafore Pharmaceuticals Inc.**'s SF 1126, a PI3K/mTOR (mammalian target of rapamycin) inhibitor in Phase I in solid tumors are pan-selective, but VC money lately seems more focused on companies working in isoform-selectivity.

One of the more advanced players in that field is Seattle's **Calistoga Pharmaceuticals Inc.**, which has two isoform-selective candidates in clinical development, another in preclinical development, and a discovery program for additional isoform-selective PI3K inhibitors. (See "Calistoga Pharmaceuticals Inc.," *START-UP*, June 2008.) On the strength of its advancement of CAL 101 and CAL 263, Calistoga raised \$30 million in a Series B round this past May, funded by its existing investors—Alta Partners, Amgen Ventures, Frazier Healthcare, and Three Arch Partners.

The two lead programs are PI3K delta inhibitors, with CAL 101 in Phase I in hematological cancer and CAL 263 in Phase

I asthma, rheumatoid arthritis, and inflammation. The CAL 263 program is slated to reach Phase II next year, the company says. So far Phase I data for CAL 101 have been impressive, according to Calistoga CEO Carol Gallagher, PharmD. “We believe Calistoga has a well-differentiated position in the space with clearly robust clinical data of about 50% overall response,” she says.

A more recent entrant into the isoform-selectivity arena is UK-based **Karus Therapeutics Ltd.** The biotech, which announced a research collaboration with **Queen Mary, University of London** in late September, is advancing two programs, one in cancer and the other in immune-inflammatory disorders, into full preclinical work by mid-2010, with entry to the clinic anticipated in 2011.

In an e-mail exchange, the company said it was not disclosing which PI3K isoforms it is targeting nor any specifics about its compounds. “We believe that our approach is unique and is focused on a particular selectivity profile against two or more PI3K isoforms,” Karus stated. Since spinning out of the University of Southampton—the result of a joint initiative with Cancer Research UK—the company has raised £2.6 million (roughly \$4.2 million) from investors including IP Group, Esperante Ventures, and New Hill Management. Besides PI3K, Karus is also developing HDAC inhibitors.

Another leader in isoform-selective PI3K development is privately held **Intellikine Inc.**, profiled in this issue, which is on the verge of taking one, maybe two, of its programs into clinical development in the next year. Intellikine recently closed a Series B that could bring the San Diego firm \$51 million over two tranches. Novartis Bioventures Ltd. led the round, with participation from US Venture Partners, **Biogen Idec Inc.**, and FinTech Global Capital. The first closing grossed \$28.5 million, and Intellikine can bring in another \$22.5 million by meeting performance-based milestones. CEO Troy Wilson says the money, anticipating that the milestones are earned, should last through 2012.

“The reason we started the company is we believe selectivity is key,” he says. “You have to hit enough targets and hit them hard enough that you get efficacy, but you don’t want to drag in so many things that you end up bringing along undesirable toxicities.”

While Intellikine is developing oncology programs, like Calistoga and others in the field, it sees significant potential for PI3 kinase inhibitors in autoimmune disease, as well. Wilson notes that PI3K delta and gamma are the “twin sisters” of signaling in immune cells and are co-expressed in most major cell types seen in the immune system.

Intellikine’s lead program is an mTOR inhibitor for cancer that is expected to reach Phase I in the next six months, says Abingworth’s Haas, a member of Intellikine’s board of directors. Abingworth, CMEA Capital, and Sofinnova Ventures led the biotech’s \$12.5 million Series A round in 2007.

Beyond that lead program, Intellikine’s focus is on bringing a PI3 kinase delta/gamma dual inhibitor for inflammatory diseases such as rheumatoid arthritis into the clinic in the next year. Succeeding in this therapeutic area likely will depend on being able to hit the delta and gamma kinases, while avoiding mTOR, which can be immunosuppressive, and alpha and beta, which can impact glucose and insulin levels.

“Selectivity as a whole becomes critically important—you’re anticipating the patients are going to be taking [these drugs] for years to decades, so don’t hit them with what you don’t have to hit,” Wilson says. “We have this phrase that we use about being able to ‘dial in’ or ‘dial out’ isoform selectivity—we can do that now with a very high degree of confidence.”

On the other side of the divide, **Arno Therapeutics Inc.**, also profiled in this issue, is working in the pan-selective field. In August, the New Jersey biotech initiated dosing in a Phase I trial of AR-12, a PDK-1 inhibitor targeting the PI3K/Akt pathway, in adult patients with advanced or recurrent solid tumors or lymphoma.

Last year, Arno raised nearly \$18 million in a private placement to undisclosed investors, and then went public through a reverse merger with Laurier International, a former educational learning materials company.

Others are embracing both pan- and isoform-selective strategies. Sanofi and Exelixis are testing pan-selective clinical-stage compounds in combination regimes and as solo agents (as part of the companies’ agreement, Exelixis is driving development and Sanofi foots the bills).

But the two companies also are working together on preclinical R&D of isoform-selective PI3 kinase inhibitors. “The goal of that part of the collaboration is to combine forces and build on what we see as a competitive lead in terms of isoform-selective programs around PI3K alpha and beta,” Morrissey says. Exelixis also is free to develop its own programs in PI3 kinase delta and gamma targeting, he added, and is pursuing such work independent of Sanofi.

Morrissey is confident both strategies could pay off. “There were some preconceived, almost dogmatic, concerns that inhibitors of this pathway might be too toxic,” he says. “For example, the insulin receptor signals through PI3 kinase, and there was a big concern that if you inhibit this pathway broadly, you might actually induce a variety of diabetic-type complications.”

“Our data and data from others would suggest that that’s not really an issue in the clinical setting, but you have to ask the question, take the compounds into man, and find out,” Morrissey adds. Data from the companies’ clinical programs should emerge at clinical meetings later this year. Wilson agrees to a point that a pan-selective approach can work in oncology because “cancer patients will tolerate a lot.” But with the trend toward combination therapy in cancer, producing drugs with clean safety and side-effect profiles remains vital, he added.

Although there are many players in the PI3 kinase space, both Abingworth’s Haas and CMEA Capital managing partner Karl Handelsman, also a member of Intellikine’s board, say they are placing only one bet—on Intellikine and the “dial in, dial out” approach of isoform-selectivity. “We feel that in this space, you have to choose a horse,” says Haas. “There are some other spaces, antibodies or protein kinases for example, where you could have multiple bets.”

Abingworth believes its faith in Intellikine was validated by last year’s transaction in which **Roche** acquired privately held **Piramed Ltd.** for \$175 million. Piramed brought two clinical oncology programs to Roche—GDC-0941, a PI3 kinase alpha inhibitor in Phase I for solid tumors and non-Hodgkin’s lymphoma, with a plan to move into Phase I in metastatic breast cancer and metastatic NSCLC, as well as GDC-0980, also a PI3K alpha

compound, which has reached Phase I in NHL and solid tumors. (See Exhibit 1.)

Also providing validation was another 2008 deal, this time GlaxoSmithKline PLC acquiring access to Cellzome AG's Kinobeads kinase-targeted platform in an option deal that provided the biotech \$25.3 million up front, with the potential for \$207.2 million in milestone payments plus double-digit royalties on net sales of produces reaching market.

The Roche/Piramed transaction “made us feel good about our investment because one of the three or four players in the protein kinase space, at least among small private companies, had been taken off the table,” Haas notes. “That probably increases the value of the remaining companies, and Piramed also was taken off the table at a pretty early stage for a pretty high valuation.” Merlin Biosciences and JPMorgan, Piramed's two investors, indeed made a solid return based on their £10 million (then valued at \$17 million) investment.

Despite a few alliances and an acquisition, the majority of dealmaking in the PI3 kinase space likely has yet to occur. CMEA's Handelsman also concedes that the debate between pan-selective and isoform-selective inhibitors remains to be determined.

“I would say that the space in general is on the early side,” he says. “There are some compounds that are in the clinic and there are going to be more. But it's not obvious what is the best and smartest thing to do. So rather than polishing the corners, each of these companies is going out and blazing new ground.”

[A#2009900203]

— JOSEPH HAAS

RELATED READING

Ahead of ASCO, Exelixis Inks Lucrative Deal with Sanofi for Its PI3 Kinase Inhibitors, *The Pink Sheet DAILY*, May 28, 2009 [A#14090528001]

Calistoga Pharmaceuticals Inc, *START-UP*, June 2008 [A#2008900126]

ACCESS THESE ARTICLES AT OUR ONLINE STORE: www.windhover.com/article

Exhibit 1

Companies Playing In the PI3 Kinase Inhibitor Space

COMPANY/ COMPOUND	INDICATION	DEVELOPMENT PHASE
Arno Therapeutics		
AR-12 PI3K/Akt	Solid tumors, lymphoma	Phase I
AstraZeneca		
AZD 6482 PI3K beta	Thrombosis	Undisclosed
Calistoga Pharmaceuticals		
CAL-101 PI3K delta	Hematologic cancer	Phase I
CAL-120 PI3K beta/delta	Solid tumors	Preclinical
CAL-263 PI3K delta	Asthma, Rheumatoid arthritis Inflammatory disease	Phase I/II
Cellzome/GlaxoSmithKline		
PI3K gamma	Rheumatoid arthritis Asthma	Preclinical
PI3K delta/gamma	Rheumatoid arthritis Asthma	Discovery
Exelixis/Sanofi-Aventis		
XL 765	Glioblastoma NSCLC Solid tumors	Phase Ib/II Phase Ib/II Phase I
XL 147	NSCLC Solid tumors Solid tumors	Phase Ib/II Phase Ib/II Phase I
Intellikine		
INK128 mTOR C1/C2	Oncology	Preclinical
PI3K delta/gamma	Inflammatory disease	Preclinical
PI3K delta/gamma	Oncology	Preclinical
PI3K alpha/beta	Oncology	Preclinical
Karus Therapeutics		
KAR-4000	Cancer and inflammation	Preclinical
Novartis		
BEZ 235	Colon, breast, prostate cancer	Undisclosed
Paloma		
Palomid 529	Ophthalmology/ Oncology	Preclinical
Roche/Genentech/Piramed		
GDC-0941 PI3K alpha	Oncology, solid tumors, Non-Hodgkin's lymphoma	Phase 1
	Metastatic breast cancer Metastatic non-small cell lung cancer	Preclinical
GDC-0980 PI3K alpha	NHL, solid tumors	Phase 1
S*Bio		
PI3K/mTOR	Oncology	Undisclosed
Semafore Pharmaceuticals		
SF 1126 Pan PI3K/mTOR	Solid tumors	Phase I
Wyeth		
PKI-179	Oncology	Preclinical
PKI-587	Oncology	Preclinical

SOURCE: Company reports