

## BIOTECHNOLOGY

# Intellikine Inc.

## *Inhibiting PI3K enzyme isoforms*

When scientists talk about pursuing disease pathways, they don't necessarily mean they are following clearly defined routes. Pathway research tends to be an exploratory process by which investigators try to unravel the series of molecular events that lead to pathologies.

In the laboratory as in life in general, however, the key junctures and actors are not always obvious. How to respond when these do appear is likewise often less than clear. So it is with the PI3K pathway, where a stampede of academic and industrial scientists is searching for targets to intervene in cancer and other diseases.

"Everybody acknowledges there's a drug in this pathway, if we can just figure it out," says Troy Wilson, the president and CEO of **Intellikine Inc.** His company, founded in January 2007 and based in La Jolla, CA, is racing against many others trying to develop inhibitors of enzymes and protein complexes within the phosphoinositide-3-kinase (PI3K) pathway.

Beyond Intellikine, the crowd of relatively young commercial competitors developing PI3K inhibitors includes **Calistoga Pharmaceuticals Inc.**, **Semafore Pharmaceuticals Inc.**, **Phoenix Biotechnology Inc.**, **Aquinox Pharmaceuticals Inc.**, and **Oncothyreon Inc.**, as well as **Arno Therapeutics Inc.** and **Paloma Pharmaceuticals Inc.**, the latter two profiled in this issue of *START-UP*.

"It's the perfect project for a start-up biotech company," Wilson declares, explaining that companies expecting suc-

cess in this space must be sophisticated in terms of chemistry and also have deep understanding of biology. Big Pharmas have begun trampling into the space, too. Some large firms like **Novartis AG** are advancing their own in-house science, while others like **Sanofi-Aventis** are hiring expert help at a hefty price. For its part, **Roche** recently acquired Piramed to obtain pertinent assets.

Unlike many areas of science and medicine, where competition rages over one specific mechanism or protein, this pathway entices with an array of choices. The PI3K enzyme has four known isoforms: alpha, beta, gamma, and delta, any and all of which are potential drug targets. The alpha isoform in particular has been widely pursued, because it is often mutated in cancers, but making an alpha-selective drug candidate has proven an elusive task. Another target hailed as highly promising within the PI3K pathway is a kinase protein known as mTOR, short for "mammalian target of rapamycin." Rapamycin is a potent antibiotic that decades ago transformed transplant

medicine by helping to prevent rejection of organs by the immune system. These days, the drug's long history is helping scientists explore the PI3K pathway. "We're guided by the rapamycin data, but this next generation of compounds work via a different mechanism, so we hope they'll make a bigger impact on cancer," Wilson notes.

Researchers around the world increasingly see mTOR as a central regulator of key functions such as cell metabolism, cell pro-

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**Business:** PI3K inhibitors as treatments for cancer, inflammation, and autoimmune disease

**Founded:** January 2007

**Founders:** Kevan Shokat, PhD; Zachary Knight, PhD; Yi Liu, PhD; Pingda Ren, PhD, VP, Chemistry; Troy Wilson

**Employees:** 22

**Financing to Date:** \$63.5 million

**Investors:** Sofinnova Ventures; Abingworth Management; CMEA Capital; Novartis Venture Funds; US Venture Partners; Biogen Idec; FinTech Global Capital

**Board of Directors:** Michael F. Powell, PhD (Sofinnova Ventures); Karl Handelsman (CMEA Capital); Ken Haas, JD (Abingworth Management); Markus Goebel, MD, PhD (Novartis Venture Funds); Troy Wilson

**Scientific Advisors:** Kevan Shokat, PhD (Howard Hughes Medical Institute, University of California, San Francisco & University of California, Berkeley); Simon Campbell, PhD (formerly Pfizer); Kapil Dhingra, MD (formerly Roche); Gary S. Firestein, MD (UCSD); David Fruman, PhD (University of California, Irvine); Stephen V. Frye, PhD (University of North Carolina, Chapel Hill); Zachary Knight, PhD (Rockefeller University); Patrick J. Murphy, PhD (Butler University); Neal Rosen, MD, PhD (Memorial Sloan-Kettering Cancer Center); Richard M. Soll, PhD (WuXi PharmaTech); Bart Vanhaesebroeck, PhD (Barts & London Medical School); Mark Velleca, MD, PhD (CGI Pharmaceuticals); Michael C. Venuti, PhD (BioSeek Inc.); Ming-Wei Wang, MD, PhD (Shanghai Institute of Materia Medica)

liferation, and angiogenesis. The molecule frequently links up with other intracellular proteins, and consequently mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) are two of the hottest targets in biotechnology today. Awareness that interfering with a molecule vital to many normal cellular functions could cause unwanted

side effects isn't dimming scientists' enthusiasm for these targets by much.

Troy Wilson says Intellikine's current lead compound INK128 inhibits both mTORC1 and mTORC2 and is, therefore, termed a dual TORC1/2 inhibitor, in contrast to rapamycin, which primarily targets TORC1. The company is pushing to get INK128 into "a fairly large Phase I/II human trial" in 2010, Wilson notes. He says compounds that inhibit these targets have anti-angiogenic properties that make them well-suited for oncology, but could also make them good for treating certain disorders of the eye, such as age-related macular degeneration. Once the company establishes a maximum dosing level, Wilson expects to evaluate the TORC inhibitors in three cancer subtypes.

"Based on what we know of rapamycin and the genetics of the PI3K pathway, we think the TORC1/2 inhibitors could treat renal cancer and endometrial cancer," Wilson observes. Still, he muses, "The question is where are you going to see some activity and where are you going to have a home run?" Signaling and xenograft data suggest the compounds could treat sex-linked tumors, such as those that arise in ovarian, prostate, and breast tissue. Hematologic cancers such as multiple myeloma and lymphoma might also respond to mTOR inhibition, Wilson says. Many researchers have noted that solid tumors have different biology than free-floating tumors, he points out, and he believes data Intellikine has developed in leukemia models are promising.

Beyond its lead program on TORC1/2, Intellikine is also developing a portfolio of compounds capable of selectively inhibiting different PI3K isoforms. The start-up has already discovered selective compounds against each target and has the ability to mix and match components to achieve a variety of therapeutic goals.

"Each one of the isoforms has a special role to play in disease," Wilson asserts, adding, "We have to place our bets and go for the profiles with the greatest impact." Preliminary data suggest that dual inhibitors of the delta/gamma isoforms display a steroid-like profile, and so could become useful anti-inflammatory drugs, he notes. Not too far behind the lead TORC1/2 program, Intellikine expects that its PI3K delta/gamma program will yield a second clinical asset in 2010.

"We're trying to look forward 10 to 15 years, to develop compounds that will be well tolerated and used widely in combination with other drugs," Wilson explains.

He figures an alpha-isoform inhibitor, which no researchers as yet have been able to produce, "would almost certainly be used in combination with other drugs," because the mutation is so prevalent. That kind of compound might be accompanied to market by a companion diagnostic meant to screen for relevant mutations, he suggests.

Although no company can claim utterly dominant intellectual property on the PI3K pathway, Wilson says Intellikine has

patented both the chemistry and biology of selective inhibitors. The company has other significant advantages as well, he contends, not least of which is "privileged access" to crystal structures of all four enzyme isoforms. Structure-guided drug discovery has been a key part of Intellikine's strategy from the outset. This approach is now fairly traditional, Wilson acknowledges, but he says, "It's do or die. We iterate faster than anyone I've seen, and we are absolutely focused on developing the world's best inhibitors of these targets."

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Key to Intellikine's speed is a unique relationship with a wholly separate company called **Chemikine**, established in Shanghai, China by Intellikine's founders and under exclusive contract to it. The group is extremely productive, Wilson asserts, and flexible enough to shift from making trial compounds one week to producing 100-gram quantities of an intriguing compound the very next week. "The arrangement has far exceeded our expectations," he says, noting that "it's a model many people would like to emulate." The outfit is managed by Pingda Ren, one of the start-up's co-founders. A Chinese national familiar with the language and culture, Ren was previously employed by the Genomics Institute of the Novartis Research Foundation and is now Intellikine's VP of chemistry.

Intellikine boasts a truly distinguished roster of executives, investors, and advisors. The company does not formally convene meetings of a scientific advisory board, but instead it calls on experts for key advice to keep projects moving forward at a fast clip. Until recently, Intellikine has been concentrating on moving compounds from the lab into the clinic. It has also engaged several business advisors, who are working with the team to monetize the assets.

Intellikine also happens to be one of the best-capitalized start-ups in the biotech industry today. The Series B financing round of \$51 million that closed at the end of June 2009 brought the company's total financing commitment to \$63.5 million. Slightly less than a third of that will be paid out as milestones are achieved, and more investors await a chance to put their money behind the organization.

As Troy Wilson sees it, Intellikine's main challenge going forward stems from the fact that, "This is a fiercely competitive field and we're burning cash. We're not going after me-too iterative compounds. We're going after best-in-class drugs for serious diseases, and we do so knowing we have a finite amount of money and time in which to create real value for patients and for investors." So far, so good.

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—DEBORAH ERICKSON