UCSF TRACS™ Translational Case Studies

CASE THREE

Intellikine

Summary

Intellikine was founded in 2007 and brought three drug candidates to clinical trials in a remarkable four years before being acquired by Millennium Pharmaceuticals in 2012. As of 2015, two of its drugs are moving through clinical trials as part of Millennium's portfolio, while the third one (duvelisib) was licensed out to Infinity Pharmaceuticals and is in a phase III trial in patients with chronic lymphocytic leukemia. Intellikine's success story illustrates several noteworthy points. The founders assembled a team with a combination of scientific and business expertise, and recruited a chief executive officer (CEO) to help develop a business plan and negotiate deals before obtaining any venture funding. Once funded, the company accelerated and lowered the cost of their drug-development program by partnering with a contract research organization (CRO) in China. Intellikine's strategic approach to raising capital and entering into partnerships contributed to their success in a very competitive and fast-paced environment, as did the co-founders' active management of intellectual property (IP).

From cutting-edge cancer research to pitching a company

In the late 1990s, Frank McCormick, a visionary cancer researcher and professor at the University of California, San Francisco (UCSF), was one of the first to predict that phosphoinositide-3 kinase (PI3K) would be an important drug target for cancer. His predictions stimulated UCSF professor Kevan Shokat to investigate the PI3K pathway, which ultimately led to the founding of Intellikine. The PI3K pathway is part of the broader PI3K/AKT/mTOR pathway, which plays a role in regulating the cell cycle. Specifically, PI3K isoforms are

DISCUSSION POINTS

- ***Team Formation*: Timing, CEO Hiring, and Network Effects**
- ***Strategies for Raising Capital*: Sources of Financing in Biotechnology**
- ***Partnerships and Outsourcing***
- ***Intellectual Property***

enzymes in the family of lipid kinases, with the ability to phosphorylate phosphoinositides (PIPs) on the 3' position of the inositol ring, converting PIP_2 to PIP_3, which activates AKT. The activity of PI3K is counterbalanced by the tumor suppressor PTEN which, as a lipid phosphatase, antagonizes PI3K function and consequently inhibits downstream signaling through AKT. The mammalian target of rapamycin (mTOR) acts both upstream and downstream to AKT and is active in two different protein complexes, mTORC1 and mTORC2.[1] These complexes regulate the synthesis of proteins for cellular functions such as growth control, cell proliferation, metabolism, and translation initiation (Fig. 1).

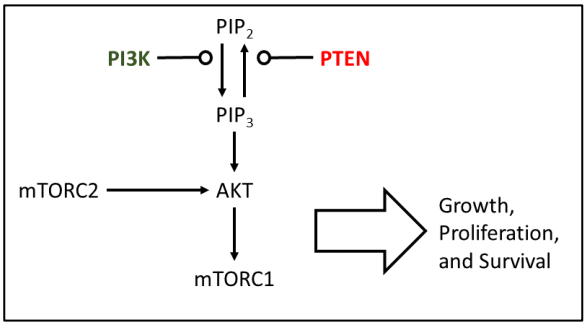

Figure 1. PI3K/AKT/mTOR pathway

The PI3K family includes many isoforms. PI3K isoform alpha is one of the most frequently mutated kinases implicated in prostate, breast, colon, brain, bladder, and lung cancers.[2] PI3K delta and PI3K gamma play key roles in inflammatory and autoimmune diseases and contribute to the survival and proliferation of cancer cells. Inhibition of these isoforms is of interest as an opportunity for targeted therapies for cancers, including hematologic malignancies, and autoimmune and inflammatory diseases. Thus, several pharmaceutical companies, such as GlaxoSmithKline, Novartis, Roche, Exelixis, and Calistoga Pharmaceuticals, started programs in the early 2000s to develop cancer drugs to block the PI3K pathway.

The first PI3K was discovered in 1988, after which more than a decade passed until the first patent applications for PI3K inhibitors were filed in 2001.[3] Selective inhibition of the PI3K pathway was a major challenge in approaching PI3K inhibition clinically. Due to the complexity of the signaling pathways, and because approximately 30 proteins are very closely related to PI3K alpha, no researchers were initially able to selectively inhibit PI3K alpha. If more than the specific isoform was inhibited, toxicity in normal cells would occur.

In the early to mid-2000s, selective inhibition of the P13K family became a major research focus in the laboratory of Professor Kevin Shokat. In 2006, Zachary Knight, then a PhD student under Shokat's supervision, was the lead author of a paramount paper describing the pharmacological map of the PI3K family.[4] In San Diego, Yi Liu, a former graduate student of Shokat's, read their papers and contacted them expressing interest in founding a company to explore the commercial development of those findings.

Liu was then a senior scientist specializing in kinase drug design at the Genomics Institute of the Novartis Research Foundation (GNF). In the same year, Shokat, Knight, Liu, and Pingda Ren, PhD, a colleague of Liu's at GNF, co-founded a company known as Kinase QuickSearch, Inc. The goal of this company was to leverage their expertise in kinase inhibitors and structure-based medicinal chemistry to provide information on pre-screened lipid kinase inhibitors to drug companies wishing to accelerate their drug discovery efforts. In Shokat's words, it was a "tool-to-drug" company. By knowing the specificity of a set of compounds against all 270 known kinases, they could suggest and sell the best compounds, enabling drug companies to start their target validation programs even before investing in any chemical research.

Also in 2006, Shokat initiated a search for a CEO before seeking funding. After interviewing several candidates, he eventually recruited Troy Wilson, PhD, JD (Table 1). Wilson completed his PhD in the same lab as Shokat, but a few years earlier, and then obtained a JD and launched a career in the biotech industry. He was the co-founder and former Chief Business Officer of Ambrx, and had been involved in the creation of several companies including Wildcat Discovery Technologies, Kalypsys, Syrrx, and Phenomix. His combination of a deep scientific background, extensive industry experience, and legal expertise made him a compelling candidate to step into this role.

Table 1. Backgrounds of the Intellikine co-founders at the time the company was founded.

Kevin Shokat, PhD PhD from UC Berkeley Professor of Pharmacology and Chemistry, UCSF and UC Berkeley Co-founder and Chairman of Scientific Advisory Board of Intellikine
Troy Wilson, PhD, JD PhD from UC Berkeley Co-founder and former Chief Business Officer, Ambrx Involved in creation of Kalypsis, Syrrx, and Phenomix Co-founder, President, and CEO of Intellikine
Yi Liu, PhD PhD from Princeton University Head of Kinase Drug Design Group at GNF Co-founder of Intellikine and Vice President of Drug Design
Pingda Ren, PhD PhD from Fudan University Senior Research Investigator, GNF Co-founder of Intellikine and Vice President of Chemistry
Zachary Knight, PhD PhD from UCSF in 2006 under Shokat's supervision Co-founder of Intellikine, Member of Scientific Advisory Board

PhD - Doctor of Philosophy; CEO - Chief Executive Officer

Pivoting from a platform company to a drug company: founding Intellikine

Although Kinase QuickSearch Inc. reached a collaborative agreement with Invitrogen, they pitched three venture capital firms and found that the investors they

approached were not interested. Offering a library of pre-screened kinase inhibitors that could be sold to other companies was not considered financeable as a business enterprise. In a key meeting with investors from Abingworth Bioventures, it became clear that investors were looking for a product-focused venture with one or two promising molecules around which a drug development program could be built.

Wilson and Shokat revised the business plan based on feedback from investors and pivoted, renaming the company to Intellikine (a name suggested by Shokat's wife, combining 'intelligent' and 'kinase'). They would choose the most promising compounds from Shokat's work and build the company's drug discovery and development program around them.

At this point, Liu, Ren, and Wilson were working without pay. This was a problematic situation, since it was difficult to transition from a high pharmaceutical company salary to no income. Approximately six months into this process, Liu and his wife made a joint decision that he would be able to work for six more months without pay. Based on this, the Intellikine co-founders established a rigid deadline for obtaining funding, and the company was ultimately funded shortly before that deadline.

In 2007, Intellikine received an initial round of funding of $12.5 million from Abingworth Bioventures, Sofinnova Ventures, and CMEA Ventures.

"We took our idea to venture capitalists. They liked our team, but told us what the numbers were—what we could sell as a screening company—and that they wouldn't make their money back. They told us we should focus on making a PI3 kinase drug and we listened. That was a huge turning point and we flipped the company." - *Dr. Kevan Shokat*

Due to the challenging economic environment and his concern for investor return, Wilson was determined to spend investor resources efficiently. By partnering with Chemikine, a 15-person contract research organization (CRO) in Shanghai, China, Intellikine was able develop its large library of small-molecule drug candidates rapidly and cost-effectively. The Chemikine executives were former graduate school friends of Ren and Liu. Due to the difference in time zones, the U.S.-based Intellikine briefed the chemists in China at the end of the U.S. workday, and the work continued in China "around-the-clock." This strategy allowed them to accelerate their rational drug design and synthesis, and to achieve high-quality results at a low cost. For this same reason, the subsequent animal studies were also carried out in China.

Only six months after the company was founded, Intellikine was pursuing two drug discovery programs. These programs were based on their discovery of a PI3K gamma and delta inhibitor (INK1197) and a PI3K alpha inhibitor (INK1117). PI3K delta is not mutated in cancer. Instead, it is present exclusively in the immune system and is a very important point of restriction for both autoimmune diseases and blood cancers.[5] One of Intellikine's advantages over its competitors was that they had the crystal structure data for their initial leads. This enabled them to embark on structure-based design, which allowed them to synthesize especially potent molecules. Intellikine then went on to develop a third lead compound, INK128. Unlike other drugs targeting the mTOR pathway that impacted mTORC1 activity alone, INK128 provided greater efficacy by directly inhibiting the activity of both the mTORC1 and mTORC2 complexes of mTOR kinase. This differentiated INK128 from rapamycin and related analogs that were further along in development in other companies. INK128 was also the first inhibitor that targeted the active site of mTOR. Its greater selectivity helped to minimize side effects in comparison to rapamycin. In addition, animal models and preclinical studies demonstrated that INK128 had the potential for efficacy in a broad range of cancers.

Developing a pipeline: funding, partnerships, and clinical trials

In 2009, Intellikine obtained $28.5 million in additional funding from its existing investors, as well as four new investors: Novartis Bioventures, Biogen Idec, FinTech Global Capital, and US Venture Partners. The deal also specified that Intellikine could obtain up to $22.5 million more based on meeting key milestones.

In 2010, Intellikine launched phase I clinical trials of INK128. This was followed in 2011 by phase I clinical trials of INK1117 in patients with advanced solid malignancies. As INK1117 (a PI3K alpha inhibitor) was entering clinical trials, the company began to be approached by potential buyers. That same year, Intellikine established a global development and commercialization partnership with Infinity Pharmaceuticals. Infinity paid Intellikine $13.5 million for INK1197, a PI3K delta and gamma inhibitor, for inflammatory and oncology indications, with the possibility of additional funding if the drug candidate were to receive regulatory approval and enter the marketplace. Selling a portion of their drug development assets was a difficult decision, but one of their investors wanted Intellikine to be a company focused on cancer only, not on inflammatory diseases. This deal provided Intellikine with funding that enabled the company to move forward with INK128 (an mTORC1/2 inhibitor) and

INK1117 (a PI3K alpha inhibitor) as drug candidates.

Endpoint: acquisition by Millennium

From its inception, Intellikine's founders built the company for acquisition, a strategy that was very appealing to its investors. Intellikine's scientists were remarkably prolific and purposeful innovators, and the company's innovations were focused on a clinical and market need, with a limited and carefully chosen set of candidate molecules to meet that need.

Though Intellikine considered options other than selling the company, including going public, the cost and risks associated with these other options were tremendous, and the team was not sure that they could succeed. For example, the costs of the next phases of clinical trials would have been enormous. Wilson believed that selling the company would maximize the return to investors and result in a higher likelihood that important new medicines would make it to market to address patient needs. At first, Shokat was hesitant to sell Intellikine, believing that the team would quickly get clinical data that would enable them to reduce cost and risk by choosing the most promising program to focus on. While the clinical data were generally positive, some patients did not respond well for undetermined reasons. More resources were needed to move the compounds through subsequent clinical trials.

In January 2012, Millennium Pharmaceuticals, the subsidiary of Takeda American Holdings responsible for Takeda's global oncology strategy and development, acquired Intellikine for $190 million. The deal included an additional $120 million based on achievement of product development milestones. The partnership between Infinity and Intellikine entered under the management of Millennium, and the rest of the Intellikine portfolio remains under development by Millennium. In a separate deal in 2014, Infinity paid Millennium $5 million for an option to buy out Millennium's royalty rights for duvelisib (INK1197) for a one-time payment of $52.5 million. Just days later, Infinity signed an $805 million deal with AbbVie, in which the companies agreed to jointly commercialize duvelisib if it receives approval, sharing profits equally in the United States and abroad.[6]

Duvelisib has demonstrated clinical activity in a number of blood cancers, and Infinity has conducted clinical trials on duvelisib, including a phase III trial in patients with chronic lymphocytic leukemia. As of 2015, MLN128 (an mTORC1/mTORC2 inhibitor; formerly INK128) and MLN1117 (a PIK3 alpha inhibitor; formerly INK 1117) are in phase III and phase I clinical trials, respectively.

The Intellikine co-founders have continued working together. In 2012, Wilson, Shokat, Liu, and Ren co-founded Wellsprings Biosciences LLC, a drug discovery incubator. They joined with Dr.

Franck McCormick to co-found Araxes Pharma, the first affiliate of Wellsprings, which in 2013 entered into a partnership with Janssen Biotech to bring novel anti-cancer compounds through phase I trials.

Discussion

Team Formation: Timing, CEO Hiring, and Network effects

Intellikine's case yields several lessons regarding team formation that go beyond recruiting a team with a balance of scientific and business expertise.

Intellikine built a team before raising money, which required the co-founders to be willing to work without salary until the company was funded. Co-founders in that situation often establish personal deadlines to pivot or move on to new enterprises if their start-up company does not attract investors in a certain period of time. Moreover, an early and open discussion about salaries and expectations among the team members can help avoid future uncomfortable situations after the initial round of funding.

In this case, rather than leading the company in the early stages, the scientific founders opted to recruit a professional CEO before obtaining any venture funding. This decision was the fruit of Shokat's previous experience with founding a company in 1999. That company, Cellular Genomics, was moderately successful, but ultimately did not yield significant profits to the co-founders. This experience had impressed Shokat with the importance of having a professional CEO present to negotiate on the company's behalf during the initial rounds of funding. Shokat also felt that it was very important for the CEO to be able to understand the science. Wilson graduated with a PhD in bioorganic chemistry from UC Berkeley, and was also a lawyer with excellent negotiation and communication skills.

The flexibility of the team and their openness to new options allowed them to rapidly make the business plan changes that would bring in investor funding. The substantial trust among the founding team members contributed to their ability to decide upon and execute this pivot successfully. One factor that facilitated the high degree of trust among the team members was that they were linked together by professional relationships before the founding of Intellikine. Knight was a graduate student in Shokat's lab, Liu was a former graduate student of Shokat's who had worked closely with Ren, and Shokat and Wilson both completed their PhDs under the supervision of Peter Schultz, an eminent researcher at UC Berkeley. Moreover, Schultz was the founding director of GNF, where Liu and Ren worked before leaving to co-found Intellikine. The network effects that contributed to the success of Intellikine illustrate an important aspect of the interplay between academia and industry

that facilitates successful translational research.

Strategies for Raising Capital: Sources of Financing in Biotechnology

The sources of capital that can be used to accelerate the commercialization of academic biotech projects can be grouped into two classes: dilutive and non-dilutive funding. Non-dilutive funding is defined as financing that does not affect the ownership of the company, does not require the sale of a company's shares, and hence does not cause dilution of the holdings of the existing shareholders. Examples of non-dilutive sources of funding include government grants, such as Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants; foundations, such as the Gates Foundation and the Cystic Fibrosis Foundation; venture debt from banks; and industry partnerships involving co-development rights. Non-dilutive sources can be an excellent way to finance an early-stage biotech startup, but the amount of funding is usually limited, and in some cases the process of obtaining funding can be very time-consuming.

Traditional sources of dilutive funding include family and friends interested in supporting your project and receiving some return; angels, who are usually wealthy individuals interested in high returns; and venture capitalists, who are professional asset managers and usually invest large sums of money with the goal of obtaining a high rate of return. More recently, crowdfunding has emerged as a new way of raising dilutive money from a large number of people, typically via the internet (Fig. 2).

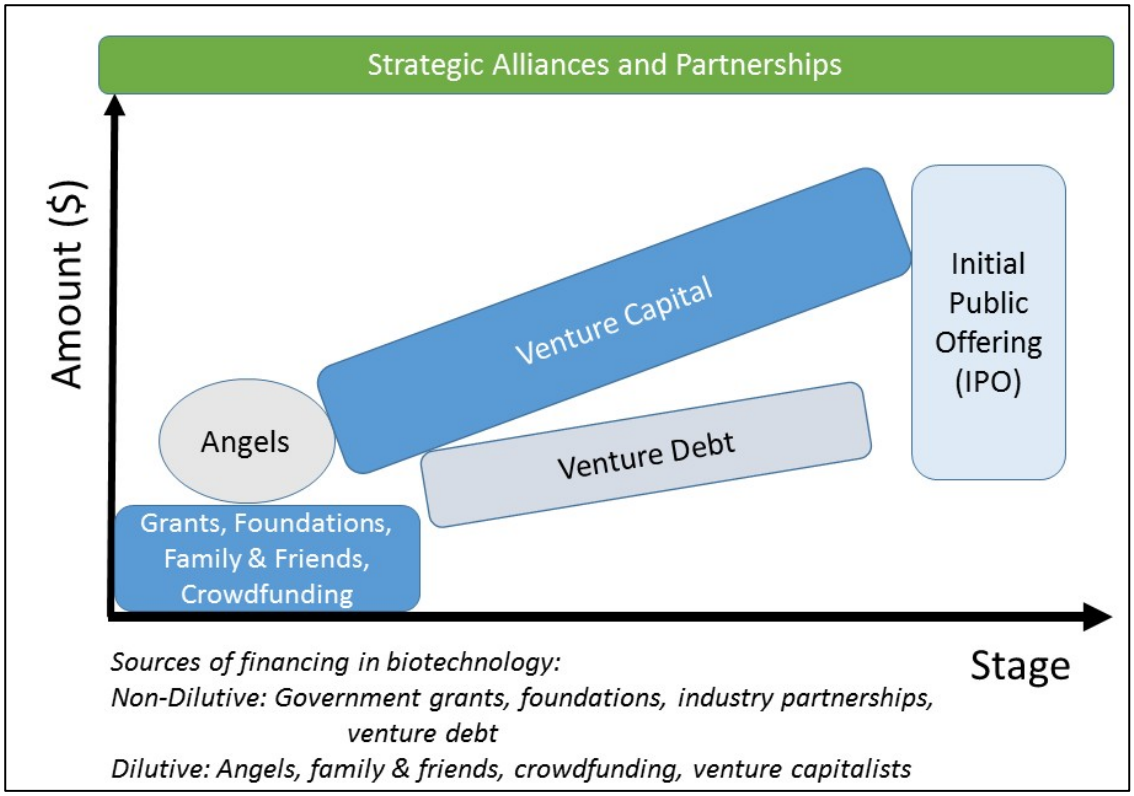

Figure 2. Sources of financing in biotechnology

The early stage of funding plays a pivotal role in shaping the further trajectory of a company. It is extremely important for founders to negotiate an advantageous term sheet. In general, everyone is rewarded if a venture is very successful, and everyone loses money when it is a failure. However, when a venture has a less than optimal outcome, the terms negotiated with the investors can make a major difference for the founders. Shokat's previous company, Cellular Genomics, was sold for only $10 million dollars more than had been invested into it, and the term sheets were structured in a way that the investors benefited when the company was sold, while the co-founders did not. In order to avoid this pitfall, Shokat decided to recruit a professional CEO for Intellikine before seeking first-round funding. Wilson's expertise not only helped in negotiating the terms, but also helped avoid the problem of overvaluation. In Shokat's words, an overvalued company has "raised too much money and then [is] saddled with doing anything possible to get out from under it."

Professional investors often request seats on the company's board of directors in order to provide guidance reflecting their management expertise and to exercise influence on major decisions and the direction of the company. The investors' experience and perspectives are usually very valuable, but they do not necessarily have as deep an understanding of the science as the inventors. This dynamic may have been at play in Intellikine's decision to license INK1197 to Infinity. That decision was difficult for the company, and the fact that Infinity and Abbvie subsequently signed an outstanding deal for this compound may suggest that the potential of INK1197 was incorrectly evaluated. Shokat has suggested that it is important for the scientists to communicate their perspectives and to push the investors to explain the logic of their decisions

Partnerships and Outsourcing

The drug-development process is characterized by long development cycles, large capital investments, and high risk. In particular, the cost of going from a target to an investigational new drug is approximately $10–15 million. Following that, roughly another $20 million is required to complete a phase II study. Thus, outsourcing or forming partnerships to accelerate or lower the cost of drug development can be desirable.

In fact, outsourcing some early stages of drug development has become widespread over the last decade. Currently, 40% of drug development expenses are projected to be committed to outsourcing, and some large companies now rely exclusively on outsourcing for certain preclinical development activities.[7] In particular, China became a particularly attractive destination for pharmaceutical outsourcing after entering the World Trade Organization and committing to the enforcement of IP protection. Due to these developments, Chinese CROs allow

pharmaceutical companies to take advantage of lower costs, skilled workers, and governmental policies favoring foreign investment in China. It has been estimated that companies can save 30%–35% by conducting certain preclinical trials in China instead of in the United States.[8]

Intellikine partnered with Chemikine, a CRO in China, in order to outsource chemical synthesis and preclinical studies. This enabled Intellikine to develop a large library of 1,500 small-molecule drug candidates and test the lead compounds very quickly and cost-effectively, given the staff and funding available. Outsourcing rapidly created tremendous value, without overspending investor funding.

"The CRO in China was a huge factor because we didn't get enough money to do all the chemistry and synthesis we needed. Two of the co-founders had friends in China. In California, we'd talk to them morning and in the evening so work never stopped. It was amazing how much science we got done." - *Dr. Kevan Shokat*

Intellectual Property

Intellikine took a proactive approach to developing a positive relationship with the University's Technology Transfer Office (TTO) and negotiated IP agreements in a way that balanced all parties' interests. The academic team successfully communicated the value of the IP to the TTO, going beyond filing disclosures to formulating drafts of the patent applications. Shokat emphasized that "this is really the job of the PI," also stating that "the university and the PI are on the same side, so you really don't want to buy into that mentality that it's you and the VC against the university—that's just not true; the VC doesn't have a third of the license share, it's the inventor's." Intellikine's active engagement with IP issues played a major role in making the company attractive to investors.

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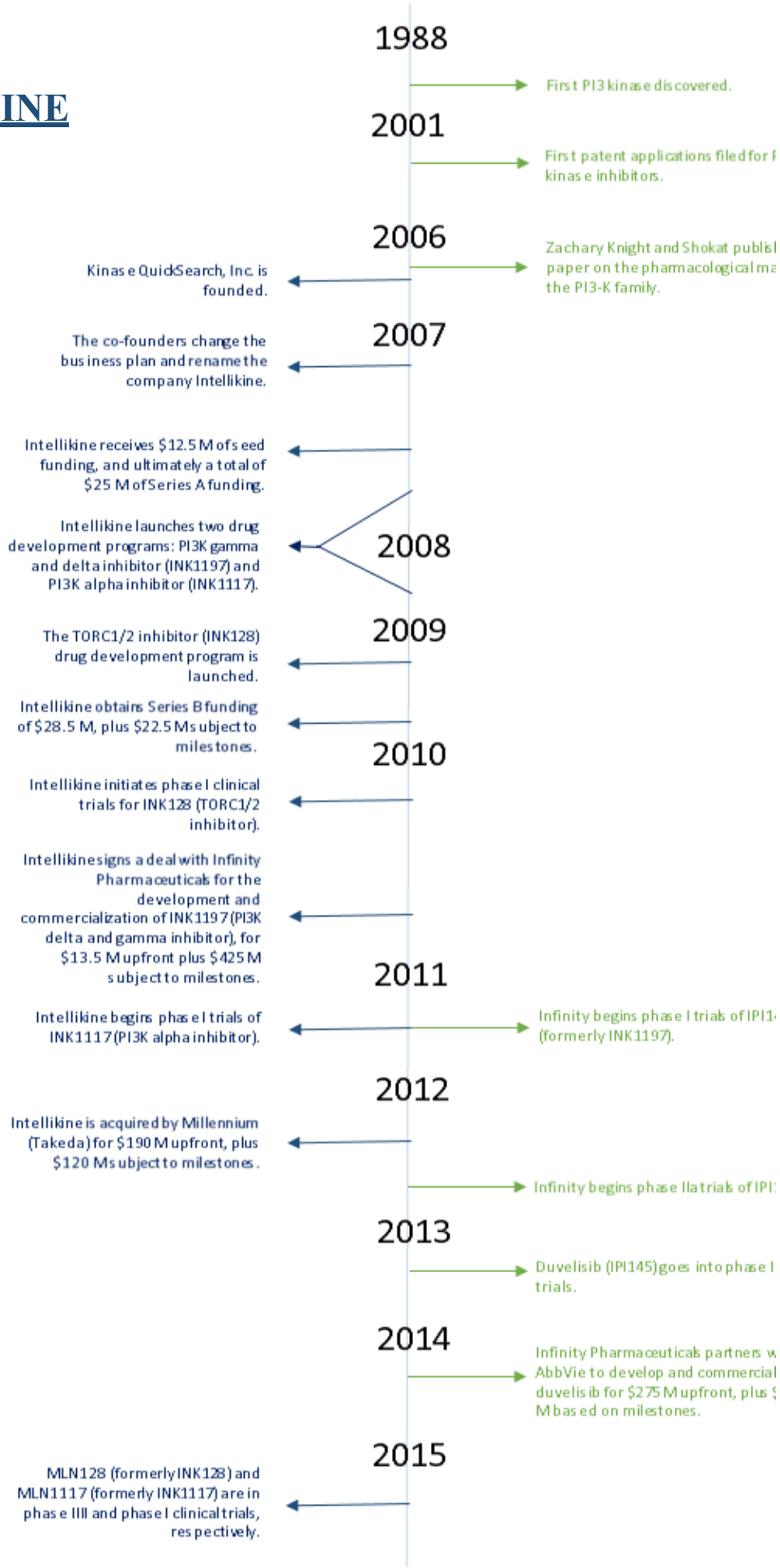
TIMELINE


1988
First PI3 kinase discovered.
2001
First patent applications filed for
kinase inhibitors.
2006
Zachary Knight and Shokat publis
paper on the pharmacological ma
the PI3-K family.
Kinase QuickSearch, Inc. is founded.
2007
The co-founders change the business plan and rename the company Intellikine.
Intellikine receives $12.5 M of seed funding, and ultimately a total of $25 M of Series A funding.
2008
Intellikine launches two drug development programs: PI3K gamma and delta inhibitor (INK1197) and PI3K alpha inhibitor (INK1117).
2009
The TORC1/2 inhibitor (INK128) drug development program is launched.
Intellikine obtains Series B funding of $28.5 M, plus $22.5 M subject to milestones.
2010
Intellikine initiates phase I clinical trials for INK128 (TORC1/2 inhibitor).
Intellikine signs a deal with Infinity Pharmaceuticals for the development and commercialization of INK1197 (PI3K delta and gamma inhibitor), for $13.5 M upfront plus $425 M subject to milestones.
2011
Intellikine begins phase I trials of INK1117 (PI3K alpha inhibitor).
Infinity begins phase I trials of IPI1
(formerly INK1197).
2012
Intellikine is acquired by Millennium (Takeda) for $190 M upfront, plus $120 M subject to milestones.
Infinity begins phase IIa trials of IPI
2013
Duvelisib (IPI145) goes into phase I trials.
2014
Infinity Pharmaceuticals partners w
AbbVie to develop and commercial
duvelisib for $275 M upfront, plus $
M based on milestones.
2015
MLN128 (formerly INK128) and MLN1117 (formerly INK1117) are in phase IIII and phase I clinical trials, respectively.

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