

## Corporate Profile:

# EXELIXIS

Exelixis is a biotech that presents an enviable pipeline of cancer compounds. It has a progressive company philosophy and big pharma collaborations. As its products reach late-stage development, the time is near for the company to deliver on their promise.

Drug development is a long, painstaking, and expensive process. Companies stand to lose millions if during the clinical phase of development the study drug fails to achieve certain milestones. Given the number of high-profile investigational failures, you have to wonder why any company would delve into the business of drug development at all. The oncology-drug market may be last growth segment of the pharmaceutical industry, and a successful development and commercialization in the \$25B cancer market reaps many years of life for a company. As biotech companies compete to develop oncology agents, they must find ways to sustain their operating expenses while their drugs mature, and in the process not suffer from any large clinical setbacks along the way.

One such company making its imprint on the biotech landscape is Exelixis, which has forged a deep, oncology-focused, small-molecule therapy pipeline. Founded in 1994 in Cambridge, Massachusetts, the company relocated to South San Francisco, California in 1997. By understanding the genetic make-up of fruit flies—which is similar to the genetic make-up humans—Exelixis has been able to leverage their findings to expand its research capabilities and fuel the growth of its proprietary drug pipeline by collaborating with big pharmaceutical companies such as BMS and GSK.

The company develops its pipeline compounds in-house, to the point where the compounds become enviable to potential partners, and then uses the unique strategy of out-licensing the compounds to form collaborations with pharmaceutical companies. A key advantage of keeping all development

in-house is that the company has an in-depth understanding of each compound. This understanding may ultimately help with claims and indications the company or licensee can get approved by the FDA, and is in line with Exelixis's strategy of out-licensing revenues to further fund development.

In the last two years, the company has filed eight Investigational New Drug (IND) applications and, according to Charles Butler, Director of Corporate Communications, Exelixis is in a position to file three INDs per year. "That productivity is competitive with any oncology group and allows us to generate high-class partnerships," he stated.

With the large volume of potential compounds Exelixis has, as well as the method of targeting a promising lead candidate, large pharmaceutical partners appear interested in collaborations. In the long run, the ultimate goal of Exelixis is to be fully integrated and to commercialize its own products, but until then it is acquiring much needed cash from forming successful partnerships.

### Forming Partnerships to Achieve a Long-term Goal

The only compound Exelixis has obtained externally, XL119 (becatecarin), was taken as payment from an earlier Bristol-Myers Squibb (BMS) collaboration, and has since been exclusively out-licensed to Helsinn Healthcare, SA, who paid \$4M upfront for the compound.

In their collaboration with BMS, combinatorial chemistry hardware and software along with related intellectual property rights were transferred to Exelixis. In return, Exelixis granted BMS a limited sublicense to use its proprietary worm and fly technologies.

The deal played a significant role in enabling Exelixis to establish a rapid and rigorous drug-screening process. Along with boosting their pipeline, the collaboration allowed Exelixis to fulfill its strategy of building its own in-house development capabilities. Other terms of the

# Big Pipeline, Big Deals, Big Promise?

By John McCleery  
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agreement included granting Helsinn worldwide royalty-bearing license while Exelixis retained the right to reacquire commercial rights in North America.

Under another agreement the company signed with GlaxoSmithKline (GSK) in October 2002, which was enhanced in January 2005, Exelixis yielded approximately \$325M in cash and commitments. Under this collaboration, Exelixis may receive milestone payments from GSK totaling approximately up to \$275M for three compounds.

The partnership assures that Exelixis will deliver a number of small-molecule compounds that have met agreed upon criteria in early Phase II trials. Exelixis will work on 12 specific compounds, while GSK retains exclusivity rights to 32 specific targets. From the 12 compounds, GSK can select up to three to choose to take forward into Phase III trials, at the completion of Phase IIa clinical development—the point at which Proof of Concept (POC) is achieved.

Enhancing the deal, GSK has also agreed to provide research funding totaling \$47.5M over the remaining terms of the agreement.

Other collaborations involve partnering with Genentech for the development of agents that target cancer, inflammatory diseases, and tissue growth and repair; and with Wyeth, to develop compounds that target metabolic and liver disorders.

Contributing to Exelixis's success with its partnerships is its compound library which numbers in the 4.3 million range, and is surpassed only by Pfizer. Exelixis builds libraries applicable to targets. A key target of interest is receptor tyrosine kinases (RTK).

RTKs are involved in cellular-signaling pathways and in the regulation of key cell functions. RTKs are also involved in more than 70 percent of known oncogenes; and when RTK enzymes are activated in a non-typical manner, such as overexpression, they can lead to a variety of cancers.

All of Exelixis's anticancer product candidates (with the exception of XL119 and XL844) are Spectrum Selective Kinase Inhibitors™ (SSKIs). These SSKIs are designed to target multiple RTKs.

## The Company's Infrastructure

Exelixis restructured in 2003-2004 and de-emphasized its agricultural and agrochemical activities, including its joint ventures with Bayer Cropscience and GenOptera. With a new direction in place, the company is focusing on product-candidate development and on growing its clinical development team.

The company's management team's proficiency and productivity is a remarkable asset which has enabled Exelixis to advance seven compounds from lead candidate to clinic in just two years. This achievement has not escaped analysts' attention.

Analysts at investment banks such as Bear Stearns, JP Morgan, and WR Hambrecht all see the next year to 18 months as a critical time frame for the company when results of the next phase of clinical POCs of several compounds now in Phase II are due. If these compounds achieve POC, Exelixis will receive significant milestone payments from GSK. The first compound approval is anticipated in 2010, which could lead the company into profitability soon thereafter. [cont. on pg 30](#) ➤

## Competition and Challenges

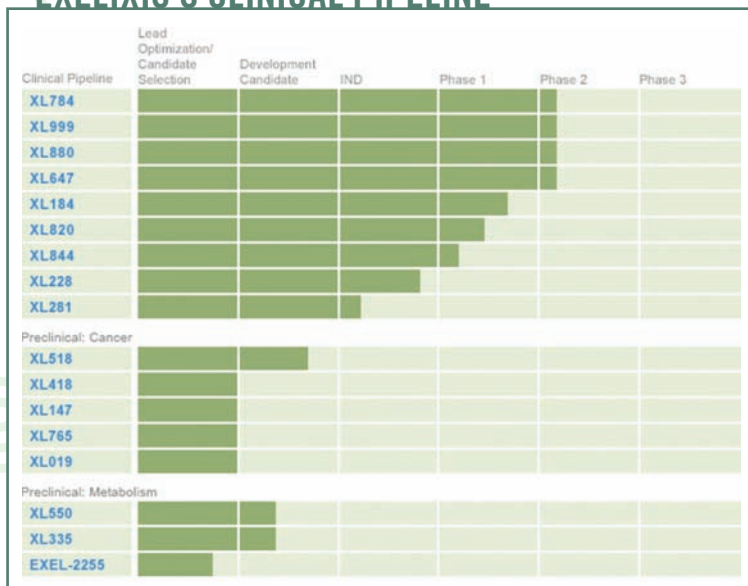
Exelixis's compound development is positioned around both low-risk targets and high-risk targets. High-risk targets being Chk and c-Met; low-risk include VEGF and HER2.

According to Patrick Flanigan, Managing Director, WR Hambrecht, Exelixis has a place among the top 10 companies working on targeted therapies. However, he indicated that the drug discovery landscape Exelixis operates in makes it difficult to differentiate their products.

“Right now, there are 83 clinical programs for signal transduction inhibitors,” says Flanigan, who also reported that several companies are pursuing similar targets that Exelixis's programs target. “Approximately 70 percent of current programs in the clinic are small-molecule based. That represents an extremely crowded field,” he said.

Exelixis's competitors include Onyx, OSI, Lexicon, and Keryx who are also developing products that interfere with cell-signaling. Despite these challenges, Flanigan believes Exelixis can compete successfully and, in fact, may be better positioned than most small companies because of its drug discovery model and clinical pipeline.

### EXELIXIS'S CLINICAL PIPELINE



Source: <http://www.exelixis.com>. Last accessed December 9, 2006.

“Exelixis comes from the approach that the first-generation targeted therapies went after one target—VEGF. But as we all know, cancer is driven by more than one signal. Exelixis's approach is not to inhibit just one target but to inhibit multiple targets,” noted Flanigan.

The premise is that by going after multiple targets, over time, clinicians will be able to avoid administering chemotherapy and avoid the related side effects caused by it. Exelixis's position is that they are producing either first-in-class or best-in-class products that will differentiate them from the competition. The answer remains to be seen, but looking at the company's pipeline, they certainly are taking their best aim at development success.

## Challenges of Compound Setbacks

One of the biggest potential downsides Exelixis faces is compound setbacks. Butler hopes for early success in trials as that will allow the company to continue on its aggressive course. However, early failure can inhibit the company's momentum and could seriously threaten its out-licensing only pursuits.

In the case with XL119, Helsinn Healthcare, SA had been conducting Phase III clinical trials in patients with bile duct tumors. Preliminary data has shown that patients in the comparator 5-FU arm demonstrated greater than expected survival—the primary endpoint. As of November 2006, enrollment for that trial has been discontinued. Butler commented that, “These results make it statistically improbable that the final study results could achieve the planned objectives.”

Compound development can also be negatively impacted by the appearance of unwanted side effects in patients during trials. During Phase II clinical trials of compound XL999, which has shown to be a potent inhibitor of FLT3, an important driver of leukemia cell proliferation in some patents with AML, data had failed to demonstrate results that would have led to Phase III studies. Patients (10%) had experienced adverse side effects which raised concerns about the safety of the compound. As a result, new enrollment has been suspended. However, for those patients already enrolled in the study with no reported cardiac toxicities, the company is electing to allow them to continue.

According to Gisela M. Schwab, MD, Senior Vice President and Chief Medical Officer of Exelixis, “We continue to believe in the potential of XL999 as a novel cancer therapy.”

Trial compound setbacks can create financial bumps in the company's aggressive forward progress. The week that the XL999 trial suspension was announced, Exelixis shares fell 11.1 percent in pre-market trading to \$8.30 from \$9.34.

## Sustaining Financial Solutions

Exelixis had its IPO in 2000 (stock symbol: EXEL) and rose \$126M. The earlier mentioned BMS deal brought in about \$180M in cash and commitments and potential royalty payments. The GSK collaboration yielded approximately \$325M. According to Form 10-K filed with the SEC in March 2006, Exelixis has about \$200M in cash and is burning about \$120M per year. The company also issued \$50M worth of stock in 2005, and in October 2006 issued 11.5 million shares at \$8.40 per share netting approximately \$90.5M.

In June of 2005, Exelixis and a private equity fund called Symphony Capital formed a joint venture called Symphony Evolution, Inc (SEI). In that agreement, Exelixis received an upfront cash payment of \$40M and another \$40M was made available to them by Symphony Capital. In exchange, Symphony obtains ownership of three drug candidates with a total of more than one million Exelixis warrants—the right to purchase stock at a predetermined price.



Source: <http://www.edgaronline.com>. Last accessed December 9, 2006.

Incidentally, GSK can select one or more of the three compounds licensed to SEI for further development at proof of concept. Giving away the rights to pipeline products is an expensive, but necessary price for a mature biotech company to pay for much needed operating capital.

## In Conclusion

With their unique corporate strategy of partnering, proprietary drug-design technology, a huge library of compounds, and a robust and enviable cancer pipeline including first-in-class candidates, it would appear as if Exelixis has it all. However, the company has already partnered their major drug candidates and has few ways to raise money while they wait for their products to mature.

In the high stakes environment of drug development, Exelixis has executed on their strategies, and their compounds have been in the development process for a number of years, however, none have produced results that would garner milestone payments.

The company is perhaps at the most critical point of its life cycle. Raising money to fund development is difficult without significant product development milestones and Exelixis is not yet self-sustaining like Amgen, Genentech, or other profitable companies that have successfully commercialized products.

In the coming year to 18 months, when data from other Phase II trials will be revealed, it will be interesting to see if the out-licensed products successfully achieve their milestones and if we'll begin to see either validation of Exelixis's technology or see another example of hype before hope.

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## FINANCIAL AND COLLABORATION TIMELINE

Month/Year	Event/Partner	Agreement/Terms
10/2006	Public Offering of Stock	\$90.5M
12/2005	Wyeth	Upfront payment of \$10M; will receive an additional \$147.5M as milestone payments
12/2005	BMS	Upfront payments, research funding and milestone payments total approximately \$167.5M
6/2005	Establishment of Symphony Evolution, Inc. (SEI)	Up to \$80M
6/2005	Helsinn Healthcare SA	Out-licensing agreement with Helsinn Healthcare SA in exchange for \$4M milestone
6/2005	Genentech	Collaboration
1/2005	GSK	Amended agreement, provided accelerated milestone payments, \$325M
6/2003	Public Offering of Stock	\$74.7M
10/2002	GSK	Formation of broad-based alliance
7/2001	BMS	In-license becatacarín (XL119)
4/2000	Completion of IPO	\$126M
9/1999	BMS	Collaboration included acquisition of BMS' combinatorial chemistry in a technology exchange