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Innovations

Exelixis: Integrated Drug-Discovery and Development Platform for Human Therapeutics

Perhaps it is not surprising, for a company whose name means 'evolution' in Greek, that since its inception in 1994 Exelixis has grown from a primarily genomics-based agricultural research venture into a drug-discovery and development company focused on finding and developing new therapies for cancer and metabolic diseases.

"We were founded in the mid-90's on genetics and genomics research involving the model systems *Drosophila*, *C. elegans*, and *zebrafish* to discover and validate novel targets for a variety of disease states," explains Michael Morrissey, PhD, Senior Vice President of Discovery. "Starting in 2000, we transitioned from focusing our efforts on target discovery and validation to a small-molecule drug-discovery paradigm with a large library of 4 million compounds and critical mass in chemistry and pharmacology," says Morrissey. "It became a classic, big pharma type of technology platform while maintaining a very aggressive biotech environment and culture."

The 500-person company based in South San Francisco, CA was launched in 1994 from the work of three primary founders: Yale University's Dr. Spyridon Artavanis–Tsakonas (now at Harvard University) and Drs. Corey Goodman and Gerry Rubin then at the University of California, Berkeley. The team focused on model-organism study to elucidate pathways potentially applicable to human biology. Exelixis was conceived as a functional-genomics company dedicated to the discovery of novel targets that could be used for drug development.

Yet, before the pharmaceutical program was up and running, Exelixis focused heavily on genomics-based agricultural research, explains Charles Butler, Associate Director of Corporate Communications. "It has proven to be a great way to leverage our technology platform so that we have the robust pharmaceutical pipeline we now have," he says. The 30-person agribusiness Exelixis Plant Sciences remains a subsidiary part of the company and is based in Portland, Oregon. Specifically, the plant business involves the study of plant genomics and plant disease resistance for the aim of developing new insecticides. But the core of Exelixis' business is now firmly planted on the pharmaceutical side.

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Spectrum-Selective Kinase Inhibitors

At the heart of Exelixis' small-molecule pipeline is a unique class of therapies involving spectrum-selective kinase inhibitors (SSKIs). "The kinase-inhibitor program is based on our fundamental understanding of key targets involved in the pathobiology of cancer and the pathways driving tumor proliferation and vessel growth (angiogenesis)," says Morrissey. For the last two years, Exelixis researchers have taken knowledge gained from functional genomics and genetics insights to bundle inhibitory activities into single molecules. The company has designed compounds that are not selective for just one kinase, Morrissey explains, but are instead spectrum-selective in that they simultaneously target several important kinases involved in tumor proliferation and angiogenesis.

Once the target kinases are determined, Exelixis uses the tools of discovery and development—high-throughput screening, combichem, structural biology, comparative genomics, chemoinformatics—to find the scaffolds and compounds giving the desired spectrum of activity in a single molecule. This approach was initially antithetical to conventional wisdom. "When we started this effort in 2002, most people wanted to have individual compounds that would be highly selective, if not specific, for a given kinase," recalls Morrissey. But tumor growth and proliferation in vivo is a polygenic process; many influences drive the broad growth and proliferation of tumors. "We believe that if you could pick and choose good combinations, you would be more likely to have much better efficacy in both preclinical and, hopefully, clinical testing," he says.

Cancer-Focused Clinical Programs

Exelixis' lead clinical candidate, XL119 (becatecarin) is not a SSKI but a topoisomerase inhibitor characterized by Bristol-Myers Squibb (BMS) and licensed in 2001 as part of a target-discovery and validation collaboration. XL119 is currently in multinational phase III trial for bile-duct tumors. "It has a fairly novel structure and is clearly doing more than just inhibiting topoisomerase," explains Morrissey. BMS characterized this compound in the NCI 60 human tumor cell line panel often used to identify drug sensitivities. "It had a different phenotype than what is normally seen with pure topoisomerase inhibitors," says Morrissey. The compound has already been tested in a large number of patients in the collaboration between BMS and the NCI, and it has shown good activity in its phase I and II studies. Recruitment for the anticipated 3-year, 600-patient phase III study began in mid-2004.

In Exelixis' largest collaboration, with Glaxo SmithKline Beecham (GSK), it is responsible for discovery and development of new drugs for cancer, up to proof-of-concept trials in phase II. The agreement involves 12 programs that include all of Exelixis' clinical candidates except for XL 119 as well as several other preclinical and lead-optimization programs. GSK has the right to select two to three compounds after clinical proof-of-concept has been achieved. Exelixis retains the rights to the other compounds.

Two compounds, XL647 and XL999, are currently in phase I studies, and there are plans to move them into phase II in the latter half of 2005. They are SSKIs designed to inhibit a spectrum of receptor tyrosine kinases. XL647, an orally bioavailable drug, simultaneously inhibits the activity of EGFR, HER-2, VEGFR, and EphB4, molecules known to facilitate tumor proliferation and vascularization. XL999 targets FGFR, VEGFR, PDGFR—key targets associated with development and maintenance of tumor vessels—and Flt3. Phase I trials with XL999 have included an IV form of the drug, although an orally bioavailable formulation is an option. In preclinical studies, XL999 has been shown to induce rapid apoptosis and tumor vascular interruption after just one dose.

XL784 is an inhibitor of ADAM-10 metalloprotease, known to be involved in blood-vessel development and proliferation. Originally developed as an anticancer compound, XL784 has been recharacterized as a therapy for patients with diabetic nephropathy because of its efficacy in preclinical models of renal failure. Phase II trials are anticipated for renal disease in 2005. XL 880 just began phase I trials. "To our knowledge, XL 880 is the most advanced orally active small-molecule inhibitor of the Met receptor tyrosine kinase, one of the hottest targets in cancer kinase research right now," says Morrissey, who explains that the inhibitor has been implicated in virtually all aspects of tumor growth, invasiveness, and angiogenesis.

Behind the compounds involved in human clinical programs are three other SSKI compounds, XL844, XL184, and XL820. XL844 inhibits CHk1 and CHk2. XL 820 acts against VEGFR, KIT, and PDGFR, and XL184 targets VEGFR2 and Met. "We expect to file INDs in the first half of 2005 for these drugs," says Morrissey. Exelixis also has three late-stage lead optimization oncology programs focused on inhibition of RAF, Akt/S6k, and IGF-1R kinases.

Generic Discovery Platform: New Targets

"The technology platform we have now is a fine-tuned small-molecule discovery engine you can use to discover drugs for any target," explains Morrissey, explaining why Exelixis is aiming its broad discovery platform to other druggable targets. "We have done a great job with kinases, but it is also very applicable to nuclear hormone receptors (NHRs) and G-protein coupled receptors (GPCRs), and we are now starting to move into those areas as well, with an intent to develop therapies for metabolic disease," says Morrissey. Known to be ligand-activated transcription factors, NHRs are involved in gene expression and have an important function in endocrine signaling. They are involved in a range of metabolic diseases, including dyslipidemias. GPCRs are transmembrane proteins and the target of more than half of all pharmaceutical compounds on the market today. They are involved in cell signaling responses to hormones, neurotransmitters, and chemokines.

"[We acquired] our NHR programs focused on Liver X Receptor (LXR) and Farnesoid X Receptor (FXR), and Mineralcorticoid Receptor (MR) after the September 2004 acquisition of X-Ceptor Therapeutics," says Morrissey.

"Nuclear hormone receptors are a completely different class of highly druggable targets," explains Morrissey. "They are the classic receptors for steroids that were once orphan nuclear receptors but are now very well known and validated to be heavily involved in a variety of diseases." The initial move into metabolic disease is an area Exelixis will pursue vigorously with GPCRs as well. Adds Morrissey, "We will have the ability to go after the three main classes of druggable targets—kinases, NHRs, and GPCRs—which is a good way to marry our powerful technology platform with the three of the most successfully drugged targets in the pharmaceutical industry."

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