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### **Blasts from the past**

**By Erin McCallister**

**Senior Writer**

While **Ligand Pharmaceuticals Inc.** s planned takeout of **Neurogen Corp.** for \$11 million in stock may look like small potatoes on paper, the acquirer thinks the deal is a key step towards its goal of becoming cash flow neutral in 2010.

For Ligand, the key will be integrating Neurogen s drug discovery capabilities with the pieces Ligand got from its purchase of Pharmacoepia Inc. last year. The goal is to produce an engine that generates about two to four discovery and/or early clinical stage programs per year.

The company plans to focus on the preclinical portion of the value chain, and thinks it can get to breakeven via a combination of new preclinical or Phase I partnerships every 12-18 months plus an influx of milestone and royalty payments from its existing later-stage partnered assets.

We do discovery work with the goal to partner at the earliest opportunity, said Ligand President and CEO John Higgins. If a target is well known and well understood, we won t wait to get human data before we partner it.

He did note the company has the capacity for Phase I and Phase II testing of compounds against more novel targets.

### **Retrograde motion**

Ligand has played in many therapeutic areas since it was founded in 1987, including metabolic diseases, cancer, pain and skin diseases. The broad focus did result in five marketed products, but never profitability. Shareholder unrest began to percolate in 2005 when hedge fund Third point, which owned 7.4 million shares (9.6%) at the time, requested three seats on Ligand s board, said it was very concerned about the company s future, and that it was not satisfied with then-Chairman, President and CEO David Robinson. In December 2005, Third Point received its three board seats.

In July 2006, Robinson resigned. That September, Ligand exited the commercial space, selling U.S. and Canadian rights to Avinza extended-release morphine to **King Pharmaceuticals Inc.** for \$265 million up front, plus royalties.

Ligand also sold its cancer drugs to **Eisai Co. Ltd.** for \$205 million in cash. Those drugs included Ontak denileuken, Targretin bexarotene capsules and Targretin gel and Panretin alitretinoin gel (*see BioCentury, Sept. 11, 2006*).

At Sept. 30, 2006, combined nine-month sales of Ligand s marketed drugs were \$102.9 million. But the company s big problem was its burn rate. Ligand posted an operating loss of \$168.8 million that year.

Higgins was brought on board in January 2007 and later that month the biotech reduced its headcount by about 76% to 85 from 352.

He refocused the company on discovery and early-stage development, with the goal of finding fully-funded partnerships for its programs at the preclinical or Phase I stage.

The company also went shopping for acquisitions. According to Higgins, candidates needed to bring two main attributes to the table: revenue-generating partnerships and discovery engines.

The company's first move was to acquire Pharmacopeia for \$54 million in stock last year. The deal checked both of the boxes: Pharmacopeia had a chemical library with millions of compounds, and multiple partnerships.

We are looking to run a company with an attractive roster of diverse, fullyfunded pharma partnerships, but also the ability to do drug discovery or incubate early research projects. Pharmacopeia brought things in each of those categories, Higgins told BioCentury.

According to Higgins, the library is the largest in the industry and the main driver behind Pharmacopeia's deals, which included alliances with **Bristol-Myers Squibb Co.**, **GlaxoSmithKline plc**, **Schering-Plough Corp.** and **Wyeth**. Those partnerships, he said, offer the potential for hundreds of millions of dollars in milestone payments, plus royalties.

Pharmacopeia had done many lucrative drug screening deals in the past few years, Higgins said. In the case of Schering-Plough, the pharma now has several compounds that Pharmacopeia had already discovered, including some in Phase II for asthma and COPD.

Pharmacopeia's deal with Bristol-Myers includes two autoimmune compounds in Phase II, while its deal with GSK has identified seven lead candidates for different indications, including inflammatory pain and respiratory diseases.

Clearly these are successful transactions in terms of what they have produced for their customers, Higgins said.

Pharmacopeia ran into problems when it failed to find a partner for its dual angiotensin and endothelin receptor antagonist (DARA) despite positive Phase IIa data. The challenge for Pharmacopeia was a competitive market environment for a program that showed an incremental benefit and dwindling cash to support the program (*see BioCentury, Oct. 13, 2008*).

While Ligand has no plans to advance the DARA program internally, it will complete the analysis of the Phase II data, look for ways to expand the patent assets and try to partner it.

Last week, Ligand made its second acquisition, agreeing to buy Neurogen for \$11 million in stock, plus more than \$7 million in potential contingency payments.

The main driver was Neurogen's vanilloid receptor 1 (VR1) program, which is partnered with **Merck & Co. Inc.**

In 2003, Neurogen and the pharma pooled VR1 drug candidates and development programs to develop small molecule therapeutics for pain and CNS indications. Merck was responsible for funding the R&D and received exclusive rights to commercialize resulting products.

The partners' lead compound, MK2295, is in Phase II testing for pain.

Ligand's potential contingency payments to Neurogen stockholders include \$3 million in cash upon Merck starting a Phase III trial for the VR1 antagonist program or 50% of the net proceeds if Ligand sells the program before the Phase III trial.

In addition to the Merck partnership, Ligand will gain Neurogen's Accelerated Intelligent Drug Discovery (AIDD) system, which uses combinatorial chemistry, high throughput screening and informatics to identify neurological disease candidates.

Founded in 1987, Neurogen also has been around a long time without a lot to show for its efforts. None of the company's internal programs have made it past Phase II. In 1997, Neurogen's NGD 95-1 NPY inhibitor showed possible dose-limiting liver toxicity in a Phase I trial in schizophrenia. The compound had been partnered with **Pfizer Inc.**

The bad news continued into this decade. In 2002, NGD 97-1, a selective inverse agonist of specific GABA receptor subtypes, showed no therapeutic effect in a Phase II trial in Alzheimer's disease (AD). That program also was partnered with Pfizer (*see Neurogen Chronicles*).

While it would seem Neurogen's lack of success would reflect poorly on its AIDD drug discovery technology, Higgins doesn't see it that way. It's not to say that their drug discovery platform doesn't work, he said.

According to Higgins, in some cases, Neurogen's compounds failed due to toxicity, while other misses were formulation-related. Ligand hopes its expertise at drug screening, which includes biologic assays for binding affinity, will eliminate some of these issues by identifying candidates that show strong affinity for the target, while also incorporating the AIDD technology to select a lead candidate.

The Neurogen technology could be used for diseases like Parkinson's or schizophrenia.

Neurogen also has an oral erythropoietin (EPO) program in early development that Higgins believes will complement Ligand's efforts (*see Ligand's Pipeline, A7*).

We have an oral EPO where we have made a lot of progress and our goal is to declare a clinical candidate in the next six months. While the Neurogen compound is further behind, it could strengthen our program and give us additional patentable technology, he said.

Neurogen's other preclinical assets include a histamine H3 receptor (HRH3) antagonist program for CNS indications, including narcolepsy.

If Ligand partners the HRH3 program, Neurogen shareholders would be eligible for \$4 million in cash or 50% of the net proceeds from the sale of IP.

### **Getting into the black**

To grow its business, Ligand is likely to do more deals like the Pharmacoepia and Neurogen acquisitions, although the company does not have a target number of acquisitions it expects to do each year.

The company expects to have nearly \$50 million in cash at the end of the year. In the absence of any more acquisitions, Ligand expects to be cash flow neutral in 2010 on an operating basis. The company has not issued guidance on when it expects to cross into the black, but Higgins thinks Ligand could become cash flow positive with its current assets.

Growing royalties, milestones or license fees will get us there. When or how we do that I believe will largely be driven by what we currently own, he told BioCentury.

Ligand has not projected how much money it expects to get from milestones and royalties it expects to accrue in 2010, but Higgins said the current estimate is that revenues next year will be similar to those in 2009.

At June 30, Ligand recorded six-month revenues of \$17.1 million.

In addition to milestone, licensing and research payments, Ligand receives royalties from Promacta eltrombopag, which partner GSK launched this year.

Ligand's two osteoporosis drugs Fablyn lasofoxifene and Conbriza bazedoxifene were approved in Europe this year. Fablyn is partnered with Pfizer and Conbriza is partnered with Wyeth. European approval triggered milestone payments to Ligand of \$3 million and \$550,000, respectively.

According to Higgins, Ligand's goal is to have two to four programs each year in discovery, preclinical and, when necessary, Phase I testing.

Based on those numbers, Ligand expects to have one partnerable asset at least every 12-18 months. Higgins said Ligand's oral EPO program or its next-generation selective androgen receptor modulator (SARM) agonist program for muscle wasting disorder are the next likely candidates for partnering.

Ligand expects data from a Phase I trial of the SARM program in 1H10.

While Higgins is hesitant to put numbers to Ligand's long term growth and revenue potential, he does believe the size and diversity of its partnered pipeline make it a sustainable, revenue generating business over the long haul.

There are peer companies that have created a royalty partnership or just royalty-based companies, but often it is just one or two royalty streams. As patents expire, investors realize it isn't sustainable because cash flows go away, he said.

In contrast, Higgins said, we have a long list of partners across a whole range of therapeutic areas and, internally, we keep adding to the shots on goal by picking targets sought after by big pharma.





