Phrixus Pharmaceuticals Inc.

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Summary:	Phrixus Pharmaceuticals Inc. aims to repurpose a compound that may be able to boost the blood-pumping capacity of damaged hearts. Carmeseal was originally developed in the 1950s by BASF as a surfactant called poloxamer-188. If results seen in several animal cardiovascular models can be reproduced in humans, Phrixus compound could become an emergency room treatment for acute decompensated heart failure.

Further Analysis:

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NellOne Therapeutics Inc.	*Start-Up*	Apr. 2010	2010900086

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Phrixus Pharmaceuticals Inc.

Helping hearts to work more efficiently

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Phone: (734) 358-9015

Contact: Leslie Browne, PhD, CEO

Industry Segment: Pharmaceuticals

Business: Therapeutic for acute decompensated heart failure

Founded: January 2006

Founders: Thomas Collet; Bruce Markham

Employees: 3

Financing to Date: $1.2 million

Investors: Private individuals; Biosciences Research and Commercialization Center; Michigan Economic Development Corp.; Pfizer Employee Retention Fund

Board of Directors: Thomas Collet; Bruce Markham; Leslie Browne; Jerry Brennan

Scientific Advisory Board: Joe Metzger, PhD (University of Minnesota); Elizabeth McNally, MD, PhD (University of Chicago); Linda Cripe, MD (Children's Hospital, Cincinnati); Hani Sabbah, PhD (Henry Ford Health Center); Steve Goldman, MD (Veteran's Administration and University of Arizona, Tucson)

Business advisors often encourage clients to "work smarter, not harder." A similar goal of enhancing efficiency – as distinct from increasing effort – is inspiring **Phrixus Pharmaceuticals Inc.** to re-purpose a compound that may prove able to boost the blood-pumping capacity of damaged hearts. If results seen in several animal cardiovascular models bear out in humans, the compound could become an emergency-room treatment for acute decompensated heart failure.

The drug candidate Phrixus calls *Carmeseal* was originally developed in the 1950s by the German company BASF, as a surfactant called poloxamer-188. By the 1990s the British pharmaceutical firm Burroughs-Wellcome decided the polymer might be a good treatment for myocardial infarction (MI), or heart attack. "Wellcome believed the compound changed blood viscosity, so that blood could be more readily pumped by the heart and better perfuse that muscle and other organs," explains Phrixus CEO Leslie Browne. That company, now part of **GlaxoSmithKline PLC**, tested poloxamer-188 on top of thrombolytic therapy in over 2,500 people at very high doses – 16 to 160 grams (not micrograms) given intravenously in an aqueous solution. The Phase II/III trial published in 1997 did not achieve its clinical end points, but scientists outside the company noted the abundance of safety data and began investigating how else poloxamer-188 might prove medically valuable.

Professor Joseph Metzger, then a physiologist at the **University of Michigan** (now Chair of Integrative Biology and Physiology at the **University of Minnesota**) found that poloxamer-188 could protect against muscle damage in the so-called mdx mouse. That animal lacks a functional gene to make the protein dystrophin, and therefore serves as a laboratory model for the human disease muscular dystrophy. Because dystrophin is a structural protein that connects the interior components of muscle cells to the cell membrane, lack of it accelerates muscle cell deterioration. Metzger found that he could induce damage in these mice by stretching and contracting muscle – and that poloxamer-188, alias Carmeseal, could counteract the effect. He then showed that the compound could even protect against death caused by the class of drugs known as beta-agonists, which stimulate the heart so much that mice given the drug die.

Metzger theorized and then showed that the repeated stretching and relaxing of heart muscle induced damage in the membranes of cardiac myocytes, by causing tears that allow calcium to leak into the cells. Browne explains that calcium's entry into cardiac myocytes is essential to heart function: increasing levels make the muscle cells contract and then the quick elimination causes the heart to relax. This process ordinarily occurs once every second or so. But when cell membranes become torn, Browne says, heart failure begins as calcium continually leaks into cells and an overload develops. "It's like trying to empty a bathtub with the faucet still on," he explains: "The heart can never fully relax, which means it also can't completely fill again, and the volume of blood pumped goes down."

Metzger's research, which even now continues spawning papers in peer-reviewed journals, intrigued Thomas A. Collet, a serial entrepreneur, who discovered Metzger's work while looking for new start-up opportunities in 2005 at the University of Michigan. Collet alerted Phrixus co-founder Bruce Markham to the work's commercial potential. Markham perceived it as a possible therapy not only for muscular dystrophy but also for heart failure. Markham at the time was a highly regarded scientist at Pfizer Inc.'s Ann Arbor research facility who had long championed collaborations on cardiovascular research between industry and academia. Markham committed to co-founding Phrixus about a year before Pfizer announced at the start of 2007 that it would close the Ann Arbor site, and lay off the more than 2,400 employees there by the end of 2008.

Soon after the company's founding, Markham and Collet began extending the research that Metzger had begun in the muscular dystrophy model to models of ischemic heart failure. The start-up worked, for instance, with a rat model with restricted coronary arteries, which was developed by Steve Goldman at the Veteran's Administration in Tucson, AZ. Hani Sabbah, of the Henry Ford Health Center in Detroit, allowed the company access to a dog model in which ischemic heart failure can be induced by injection of microspheres into the heart. When that is done in the model, the amount of blood the heart pumps, known as the ejection fraction or EF, drops to around 25% as opposed to the normal human EF of about 60 to 65%. Carmeseal has shown activity in both animal models, Browne says, and its developers both sit on Phrixus' scientific advisory board.

Browne joined Phrixus as CEO in November 2008, bringing a depth of experience that should allow him to guide the start-up through succeeding evolutionary phases. Browne started his career as a chemist at Ciba-Geigy Pharmaceuticals, then went on to hold various executive positions there and at Berlex, including running an internal venture group and heading up drug discovery for Berlex Biosciences. He later served as COO of Iconix, a chemogenomics firm, and as president and CEO of Pharmacopeia Inc.

Though the financial markets have been in dreadful shape since Browne took the helm of Phrixus, he expects his past experience working with venture capitalists will help the company negotiate a Series A round when the markets improve – and ideally arrange a small financing before that. In the meantime, he has been concentrating on getting Carmeseal ready for clinical testing. Phrixus had a pre-IND meeting with the Food and Drug Administration's cardiorenal division in April 2009, and then it did some preclinical dose-ranging studies. The company submitted all the paperwork for an IND at the end of August 2009, resulting in its being opened on October 1, 2009.

Phrixus received FDA's orphan drug status for Carmeseal as it develops a treatment for Duchenne's muscular dystrophy, a disorder affecting about 20,000 males in the US. Browne sees the drug candidate as a "significant incremental" treatment for this orphan indication, less risky than "futuristic" efforts to develop genetic or stem-cell therapies. He figures Phrixus can advance from where it is today all the way to marketing approval for the orphan indication for significantly less than $30 million.

Clearly, though, the company sees more commercial potential in developing Carmeseal as a treatment for acute decompensated heart failure (ADHF). This clinical focus is decidedly different than congestive heart failure (CHF), Browne emphasizes, and far more approachable by a start-up company. Whereas CHF is a chronic condition associated with suffering and co-morbidities that advance over years as patients' hearts lose ability to pump oxygenated blood, acute decompensated heart failure is a crisis that can kill suddenly and that brings people to emergency rooms.

In the US, heart decompensation crises are responsible for about one million hospitalizations each year. In medical terms, "decompensation" means functional deterioration of a previously working system. When the heart is decompensated, the organ can become "overloaded," full of fluid and unable to pump sufficient levels of oxygenated blood through the body. Typically, Browne says, patients receive a diuretic of some sort and a vasodilator such as nitroprusside and/or an ACE inhibitor to "unload" the heart. If that doesn't work, he says, the last step is to administer a positive inotropic agent like a beta-agonist to stimulate the heart and make it pump harder at the recognized cost of potentially shortening a patient's life.

Browne believes Carmeseal has a different mechanism of action than any of the other sorts of drugs usually prescribed for ADHF. Though scientists do not know exactly how the drug acts at a molecular level, Browne maintains that the pharmacologic data are compelling. "We've shown that our compound increased ejection-fraction volume and cardiac output, without increasing heart rate or arterial blood pressure and without increasing the force of contraction," he declares, adding, "Our compound does all these good things without making the heart work harder, but by letting it work more efficiently." Browne notes that this profile was "viewed very positively by the FDA advisory committee."

Browne is convinced that Carmeseal can bring economic as well as therapeutic benefits to ADHF patients, many of whom make an average three to four trips to hospital emergency rooms in an 18-month period. "They come in, get recompensated, then go home and back on medications. After an initial episode, up to 40% of patients are back in the hospital again or dead within 60 days." With that statistic in mind, Browne is contemplating a clinical trial with a 60-day end point. Such a limited time frame makes development affordable for a small company more than, say, a treatment for chronic heart failure that would likely require a trial with a two- or even three-year observation period. Ideally, Phrixus and its backers aim to show that Carmeseal can reduce the frequency of re-hospitalization or death, and/or time spent in hospital.

Formulating this drug candidate for intravenous use in an ER setting makes sense, because the compound is not orally available. But the theory that poloxamer-188 helps hearts by mending micro-tears does suggest it could also help patients with CHF, Browne points out: "Although the average heart failure patient is not in crisis, most of them are headed for ADHF." He muses that the compound "could be administered on an outpatient basis every few weeks to prevent general deterioration," or perhaps via a mini-pump that would be refilled every 40 to 80 days.

Although it is tempting for Browne to consider long-range development plans for Carmeseal, this seasoned biotech executive is well aware that competition is brutal in large markets like CHF. While drug candidates that others are developing and licensing may help establish benchmarks useful in discussions with VCs, for now Phrixus is focusing on what it can achieve as a small company operating in a harsh financing climate. Developing Carmeseal for muscular dystrophy, for instance, is prudent not only because it leverages founders' research and permits the orphan-drug status, but also because that focus lets Phrixus apply for specialized grants that subsidize basic work pertinent for ADHF also. Like many biotechnology start-ups, Phrixus aspires to show its compound's efficacy in a Phase II trial, then sell the asset to a big pharmaceutical player. –

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