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BIOTECHNOLOGY

Cornerstone Pharmaceuticals Inc.

Leveraging insights into cancer cells' nutritional needs

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Contact: Robert Shorr, PhD, CEO
Industry Segment: Biotechnology
Business: Drugs and a delivery method specific to cancer cells
Founded: March 2002
Founders: Robert Shorr; Robert Rodriguez, President & COO; H. Gilbert Polinsky
Employees: 16
Financing to Date: $36 million
Investors: Private individuals
Board of Directors: H. Gilbert Polinsky; Stuart Polinsky; Bernard Gross (BG Capital Management); Patrick S. Wilmerding (Althea Partners); Robert Shorr; Robert Rodriguez; David Polinsky, VP & General Counsel
Board of Advisors: Randall K. Johnson, PhD; Franco M. Muggia, MD (New York University Medical Center); Robert Weinberg, PhD (Massachusetts Institute of Technology Whitehead Institute); Gregg Semenza, MD, PhD (Johns Hopkins University School of Medicine)

Cancer metabolism was not a hot topic in 2002, when Robert Shorr, Robert Rodriguez and H. Gilbert Polinsky decided to form and seed-fund a start-up biotechnology company intent on developing novel chemical compounds and a drug-delivery method specific for cancer cells.

Now eight years later, researchers, investors and pharmaceutical executives alike are excited about the possibility of interfering with the metabolism of cancer cells. The managers of **Celgene Corp.** were enthusiastic enough to make a $130 million up-front payment in April 2010 to **Agios Pharmaceuticals Inc.**, a start-up less than two years old. The payment reportedly includes a modest equity investment, but the real buzz stems from the fact that Celgene put itself in position to option compounds after Phase I trials, and promised to pay well for the privilege of taking over worldwide development at that early stage. Growing numbers of companies are waving flags claiming to be leading the chase in the promising research area that James Watson, PhD, the co-discoverer of DNA, lauded in a *New York Times* op-ed piece in August 2009.

While the crowd gets loud, **Cornerstone Pharmaceuticals Inc.** is still saying little about its lead drug candidate, CPI-613, which entered its first Phase I/II human clinical trial late in 2008. The company and its backers believe they are developing a potentially "game-changing" class of new molecules based on an "Altered Energy Metabolism Directed" (AEMD) platform that involves an as yet unproven mechanism. Like earlier-stage start-ups profiled in this issue of *START-UP*, Cornerstone believes it has identified chemical compounds that interfere with key enzymes that allow a cancer cell – like any cell – to produce ATP and utilize the energy for differentiation and growth. Cornerstone itself has grown via private investment only, after determining back in 2002 that its insights would require years of fundamental research to flesh out – far longer than VCs are typically willing to support, even with the promise of eventually taking "high-value shots on goal."

The company posted a small abstract about its work at the *American Society of Clinical Oncology (ASCO) 2010 Annual Meeting*, but has published limited data about the activity or efficacy, or even the presumed mechanism of action, of its lead candidate. Likewise, Cornerstone has revealed next to no technical details about a lipid, oil and water nanoemulsion dubbed *Emulsiphan*, which the company licensed early on. Managers believe it can preferentially deliver many kinds of drugs to cancer cells.

"We set out to identify drug targets that would be at the core of cancer, and which thus would likely be maintained across diverse tumor types and diseases," declares CEO Robert Shorr. "We also wanted to be able to find biomarkers of prognostic or diagnostic value," he adds, "so that we could take drugs that do not have a disease-specific mechanism of action and know we are making them very specific in terms of where they are delivered." The work has progressed well, he asserts: cell-culture studies led the way to testing in animal models, and data from two early clinical studies in over 40 patients "support the design of a Phase II program" that is scheduled to commence by the end of 2010.

Before co-founding Cornerstone, Shorr was chief scientist for United Therapeutics. Prior to that, he served as VP science and technology and VP for R&D at Enzon. Earlier still, after a post-doctoral fellowship with Robert Lefkowitz, MD, at Duke University's Howard Hughes Medical Institute, Shorr filled the role of associate director of molecular pharmacology at SmithKline and French.

All of these professional and academic experiences, he reflects, put him "ever

on the prowl for metabolic links to cancer." Shorr realized during an academic appointment at the State University of New York at Stony Brook in 2000, that a research scientist there named Paul Bingham, PhD, was describing technology that offered a potentially new way to treat cancer by targeting key enzymes involved in cancer metabolism.

Shorr shared his thoughts and his excitement with his partners Robert Rodriguez and H. Gilbert Polinsky, an attorney with more than 40 years of legal experience. They, too, saw potential in the intellectual property developed by Bingham at SUNY, and together the three agreed to form Cornerstone to in-license and develop a drug candidate based on what is now the company's AEMD technology. "Other well-known companies had been shown the AEMD technology," recalls Shorr, "but at the time did not recognize its inherent value. We had all been inventors, so our tolerance for early-stage research was higher than most people's."

Cornerstone in-licensed the technology from SUNY, knowing full well it would take a long time to understand the mechanism of action and to design clinical trials to prove efficacy of a candidate molecule. But now, says Tim Sullivan, who joined Cornerstone as EVP and head of corporate development in March 2010, "Cornerstone is confident, based on our clinical trials, that our lead drug candidate CPI-613 is well tolerated. In fact, it has an extraordinary safety profile so far."

In April 2010, **Wake Forest University** researcher Timothy Pardee, MD, PhD, agreed to test CPI-613 in a mouse model of acute myeloid leukemia, and eventually in human patients with advanced hematologic disorders such as leukemia and lymphoma. In early August 2010, the **Mary Crowley Cancer Research Center** in Dallas, TX, announced that it would commence clinical trials of CPI-613, as a stand-alone agent and in combination with the frequently prescribed cancer drug gemcitabine.

In March 2010, Cornerstone and the **National Cancer Institute** agreed to collaborate on testing Emulsiphan, the company's nanoemulsion, as a delivery vehicle for novel anti-cancer agents developed at NCI. The partners are hoping that Emulsiphan will enhance penetration into tumors by compounds that the Institute's researchers intend to activate by targeted radiation and ultrasound.

Like other companies developing drug candidates meant to interfere with cancer metabolism, Cornerstone will leverage imaging techniques such as PET-glucose scans in its clinical trials. This method gives researchers a window on metabolic activity, such as cells' uptake of glucose, within known regions of cancerous tissue. While imagery can be indicative of efficacy, Sullivan says Cornerstone is mindful that FDA regulators are intent on a straightforward clinical endpoint: enhanced survival for treated patients.

"Everyone will have to use imaging at some point in clinical development," Shorr points out, but Cornerstone would prefer if commercialization efforts for its drug candidate and delivery method did not have to hinge on expensive and inconvenient technology applicable to only certain types of cancers. Because the company's drug candidates have an effect on cellular metabolism, Shorr says his team is betting it will be possible to elucidate metabolic fingerprints related to sets of biomarkers. To that end, Cornerstone has been looking at new classes of biomarkers that could "let us utilize plasma tests to determine if a treatment is working and if dosing should continue," Shorr says.

As cancer cells' nutritional requirements shift, "what they want to take up will also change," Shorr points out. This insight has been guiding Cornerstone's efforts to develop drug candidates based on both its AEMD platform and on Emulsiphan. Shorr says, "AEMD specifically utilizes this difference in metabolic appetite to facilitate selective delivery of a novel small molecule [CPI-613 being the first example] into a cancer cells' mitochondria. This organelle is the central point of certain energy production processes, and also the place where specific biosynthetic intermediates are produced. The mitochondria is thus a key participant in effecting cell death." The company's Emulsiphan platform, by contrast, is designed to leverage differences in the metabolic needs of cancer cells to deliver drugs specifically to the cancer cell cytoplasm. "We are studying the relational aspects between these molecules and the cancer cells, to learn what kinds of drugs to use when," Shorr declares.

He says Cornerstone recognizes that "any biomarkers we choose to support our drug therapy will have to be validated against the current standard of care, which includes imaging." Even so, Shorr maintains that that developing biomarkers is "a valuable goal" that has warranted years and years of research. "We are not looking to demonstrate response by the disease alone," he emphasizes. In his opinion and that of company advisors, biomarkers that are linked to a drug's mechanism of action and correlate with outcome can help guide clinicians' treatment decisions for cancer patients.

Beyond preparing biomarkers as tools to support clinical development, Shorr says Cornerstone has been concentrating on designing the next round of human studies "so that data are interpretable with the least possible torturing of statistics, and the drug's benefit is immediately apparent." If the data from the upcoming trial do not show the dramatic effect Cornerstone is expecting from its drug candidate, "we would have to revisit the dosing schedule and levels currently under investigation to optimize benefit."

Shorr says he anticipates that Cornerstone may at last be ready by the end of 2010 to reveal its drug candidate's mechanism of action, by submitting an article for publication in a high-profile scientific journal. Making the case for an entirely new class of molecule is complicated, he notes, because "the level of 'show-me' is much higher than for new drugs within an established drug class." As competing companies now pile into the field of cancer metabolism research, and Cornerstone prepares to advance CPI-613 into the Phase II portion of its clinical development program, Shorr is convinced that keeping a low profile through the past eight years was the right thing to do: "Staying off the grid has been necessary to protect the high potential of our research."

To date, Cornerstone says it has received $36 million in investment, mainly from private individuals.

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— Deborah Erickson