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Strategy

Leaving cancer behind

By Michael Flanagan
Senior Writer

Faced with a decision about how best to utilize its platform technology targeting the cytoskeleton, **Cytokinetics Inc.** initially chose cancer as the path of least resistance for attracting investors and partners. Ten years later and without a breakout success in oncology, the company last week said it will restructure and refocus on muscle biology, an area that has received an increasing amount of in-house investment and produced one clinical candidate, with more close behind.

Cytokinetics was founded in 1997 based on the idea of targeting specific motor proteins involved in the cytoskeleton that play crucial roles in cellular processes as varied as intracellular transport, cell division and motility; signal transduction; and the establishment and regulation of cell polarity.

The cytoskeleton is believed to play a fundamental role in both cell proliferation and muscle contractility. This led the company to identify cancer and muscle biology early on as the two areas of human physiology most amenable to intervention with small molecules against cytoskeletal proteins, CEO Robert Blum told BioCentury.

Given the technology's broad applica-

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bility, the dilemma was charting a course that the company could reasonably pursue with the resources of a fledgling biotech. Cytokinetics decided to focus its initial efforts on cancer, where it thought programs would be easier to monetize, and succeeded in signing a partnership with **GlaxoSmithKline plc** that paid for much of its early stage work.

“Back in the 1990s and early 2000s a lot of cancer companies were formed be-

cause investors and entrepreneurs thought the space offered a faster, less expensive and more reliable path to approval,” said Blum. But the field has become far more crowded and the regulatory environment less certain.

In cancer, Blum noted, “the cost per patient in a Phase II trial has more than doubled from \$20,000-\$25,000 to something closer to \$50,000-\$60,000, while the patients being enrolled in trials are increasingly chemo-refractory and difficult to treat. The regulatory environment is also much different now than it once was, with what is sufficient for approval becoming less clear.”

Blum added that Cytokinetics always has been mindful of the importance of diversifying risk.

“As a biology-centric company that for over 10 years has been mining biology of the cytoskeleton, we set out long ago to investigate a number of different pathways and targets that could take us in multiple directions without being beholden to any one pathway or disease area,” he said.

The company's strategic review “pointed to the fact there may come a day where, because of constraints in the capital markets and partnering, as well as successes in the development-stage readi-

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Muscle biology applications

Cytokinetics (NASDAQ:CYTK) is developing small molecule activators of cardiac and skeletal muscle and inhibitors of smooth muscle with the goal of repairing faulty muscle contractility. Below is a list of indications that Cytokinetics believes its cytoskeleton-based technology platform has the potential to address.

Cardiac	Skeletal	Smooth
Acute heart failure	Amyotrophic lateral sclerosis (ALS) Cachexia Claudication Muscular dystrophies Sarcopenias Spinal muscular atrophy	Asthma Chronic obstructive pulmonary disease (COPD) Pulmonary arterial hypertension (PAH) Systemic hypertension

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ness of our work in muscle biology, we may be forced to approach our areas of focus a little differently,” Blum noted.

Indeed, he said the company had been “dialing up” its spending on R&D in muscle biology while in parallel “dialing down” in antimetabolites. “For the last two years, close to 70% of our R&D spend has been dedicated to our work in muscle biology, which was done purposefully in order to diversify risk beyond oncology given how crowded, expensive and uncertain cancer drug development has become,” Blum said.

Last week the company announced it would drop discovery research in cancer and focus exclusively on identifying small molecules for diseases related to muscle biology. As part of the shift, Cytokinetics will reduce headcount by 45 (29%) to 111, with the cuts coming primarily in G&A and early oncology research.

Blum believes Cytokinetics’ technology has the potential to churn out multiple candidates for a range of diseases related to contractile function of cardiac, skeletal and smooth muscle systems (see “Muscle Biology Applications”).

The first compound to emerge from the company’s muscle biology program, CK-1827452, is in Phase IIa testing to treat heart failure.

Act 1: Cancer

According to Blum, cancer initially looked to be “the low hanging fruit” because of promising preclinical data for the company’s kinesin spindle protein (KSP) program, combined with interest from investors and potential partners. In addition, drugs such as the taxanes and vinca alkaloids already had validated the strategy of disrupting mitosis to treat cancer,

though Cytokinetics believed targeting specific motor proteins might avoid side effects such as peripheral neuropathy.

“Our initial focus was on discovering and then developing antimetabolites as anti-cancer chemotherapeutics, which produced our first three clinical candidates and helped the company get financed early on, do our first deal, do an IPO, and build out into a more robust company,” said Blum.

This first deal came in 2001 when Cytokinetics and GSK partnered to discover and develop inhibitors of mitotic kinesins, which are cytoskeletal enzymes that act in concert to form and operate the mitotic spindle during cell division. A pair of KSP inhibitors emerged from the collaboration and eventually reached the clinic, including ispinesib (SB-715992) and SB-743921.

Thanks in large part to the increased bandwidth provided by money and clinical support from GSK and with help from the **National Cancer Institute**, Cytokinetics was able to evaluate ispinesib in a total of three Phase I, three Phase Ib and nine Phase II trials for a variety of cancers. The Phase II program evaluated the agent in breast, colorectal, head and neck, hepatocellular, hormone-refractory prostate, melanoma, non-small cell lung and renal cell cancers.

While ispinesib demonstrated some activity in a number of tumor types, most notably breast, non-small cell lung and ovarian cancers, Cytokinetics did not see the level of efficacy necessary to move directly into Phase III testing.

“In late-stage patients we saw a 9% response rate, which is comparable with a number of now marketed agents, plus our product had a much better tolerability profile. But before investing the many tens of millions of dollars or more in registration trials we wanted to see if we could

maintain the favorable tolerability with a more dose-dense schedule in earlier-stage patients,” said Blum.

“We now know that we have a well tolerated agent that shrinks tumors, the question now is does it shrink tumors in a large enough population and are the responses sufficiently durable to warrant progression into Phase III testing,” he added.

To answer this question, the company began a Phase I/II trial earlier this year to evaluate the new dosing regimen of ispinesib as monotherapy in chemotherapy-naïve patients with breast cancer. Earlier this month, Cytokinetics presented interim data showing one partial response and three cases of stable disease among 13 evaluable patients.

Meanwhile, SB-743921 is in Phase I/II testing for non-Hodgkin’s lymphoma (NHL). GSK has an option to co-develop both the KSP inhibitors and is expected to make a decision about whether to opt in on each program by year end.

Cytokinetics also has an option to co-develop GSK-923295, a small molecule inhibitor of centromere-associated protein E (CENPE) for which GSK is leading development. The compound is in Phase I testing for solid tumors.

While Blum stressed that last week’s shift would not affect its commitment to developing the two KSP inhibitors or supporting GSK’s work with GSK-923295, “the muscle biology franchise has eclipsed oncology in terms of offering diversified programs that extend across multiple clinical indications while offering better synergies between programs than we ever had in oncology.”

Act 2: Muscle biology

According to Blum, there are many parallels between the company’s work in

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addressing the cytoskeleton for cancer and muscle biology.

"Many of the same technologies involved in identifying and optimizing small molecules against motor proteins involved in cell division are also useful in identifying activators and inhibitors of motor proteins involved in muscle contractility," he said. These include overlaps in biochemical assays, robotics and cell informatics.

Importantly, Blum noted little progress has been made in addressing many of the indications that fall under the muscle biology umbrella because the underlying science is poorly understood.

"There is no question that muscle biology is less crowded; in fact we're the only ones working in this space. The unmet need in a lot of these areas is extremely high and the regulatory requirements are much more straightforward [than cancer], plus a number of indications offer accelerated paths to approval," he said.

To that end, Cytokinetics hopes that targeting the cytoskeleton directly will address a number of historically difficult diseases. The approach targets the fundamental interaction between actin and myosin, the cytoskeletal proteins that make up the sarcomere.

The company's initial focus in muscle biology was on small molecules that enhance cardiac myosin, the motor protein that controls cardiac contraction. In 1Q04, CK-1213296 was the first candidate selected to begin preclinical development for heart failure. It was eventually shelved in favor of CK-1827452 due to its better tolerability, pharmacokinetics and potency.

A Phase I trial of intravenous CK-1827452, which began in 2005, showed a 0.5 mg/kg/hr dose given as a six-hour infusion led to a mean increase in left ventricular ejection fraction and in fractional shortening vs. placebo ($p < 0.0001$ for both).

Based on the strength of the Phase I data, **Amgen Inc.** paid \$75 million up front, including a \$33 million equity purchase, in exchange for an option to license the program after Phase IIa testing. Cytokinetics has begun a Phase IIa program to treat heart failure that consists of three trials, including two evaluating

intravenous CK-1827452 and one involving oral and intravenous formulations of the compound.

Behind the cardiac muscle program, the company has research in skeletal and smooth muscle function. "The skeletal muscle program is just a nose in front, and I expect the first IND will be for a skeletal sarcomere activator. But the smooth muscle program is just behind it, and I expect two to three INDs will be filed in the 2009 and 2010 time frame," said Blum.

In April, Cytokinetics announced it had selected a small molecule activator of the troponin complex of the skeletal sarcomere to begin preclinical development for diseases related to aging and neuromuscular wasting. The company believes activating the troponin complex will increase its sensitivity to calcium, which will lead to enhanced skeletal muscle contractility.

Blum said skeletal muscle activators have potential utility for indications ranging from muscular dystrophies and cachexia, to claudication and sarcopenia, and amyotrophic lateral sclerosis (ALS).

The company's smooth muscle program is focused on identifying small molecule inhibitors, which Blum said have the potential for addressing asthma, bronchospasm, chronic obstructive pulmonary disease (COPD) and systemic hypertension depending on formulation and how long- or short-acting the agents are.

Cytokinetics expects the restructuring to reduce operating expenses by \$12-\$16 million in 2009. It also said it expects its 2008 operating expenditures to be \$76-\$81 million. At June 30, the company had \$86.9 million in cash.

Blum said the company's financing moves will largely depend upon whether GSK and/or Amgen exercise one or both of their options. The pharma's option expires at the end of the year while Cytokinetics also will have completed the required Phase IIa trials of CK-1827452 by year end, though the amount of time Amgen has to make its decision has not been disclosed.

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.

Cytokinetics Inc. (NASDAQ:CYTK), South San Francisco, Calif.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

National Cancer Institute, Bethesda, Md.