

SECTOR WATCH: BIOTECHNOLOGY

Trying To Unlock Heart's Genetic Key

By John Galante

Fresh off a public market performance that pleased its venture backers, Myogen Inc. has spun off a start-up that promises to treat the heart on a more personalized basis.

With \$15 million of financing and a hold on an important set of clinical trial data, **ARCA Discovery Inc.** is now in full pursuit of Food and Drug Administration approval for a personalized congestive heart failure therapy, a drug aimed at a specific set of patients with a specific genetic profile.

To be sure, companies developing diagnostics or drugs aimed at patients with certain genetic make-ups have had some success in treating cancer, but advancement of such approaches has lagged in the cardiovascular space. "Cardiovascular needs to get there," said ARCA Chief Executive Michael Bristow, the Myogen founder leading this new effort.

ARCA isn't alone in this fight. **Kleiner Perkins Caufield & Byers** teamed up once again with **TPG Ventures** to start **CardioDx Inc.** Investors and the company's Chief Executive David Levison declined to discuss the venture. But it's clear the two early investors in Genomic Health

Inc., a pioneer in the oncology molecular diagnostics space, hope to repeat the story by helping cardiologists predict the risks and benefits of cardiovascular therapies through a molecular diagnostics approach. According to its Web site, CardioDx is focused in the areas of congestive heart failure and coronary artery disease.

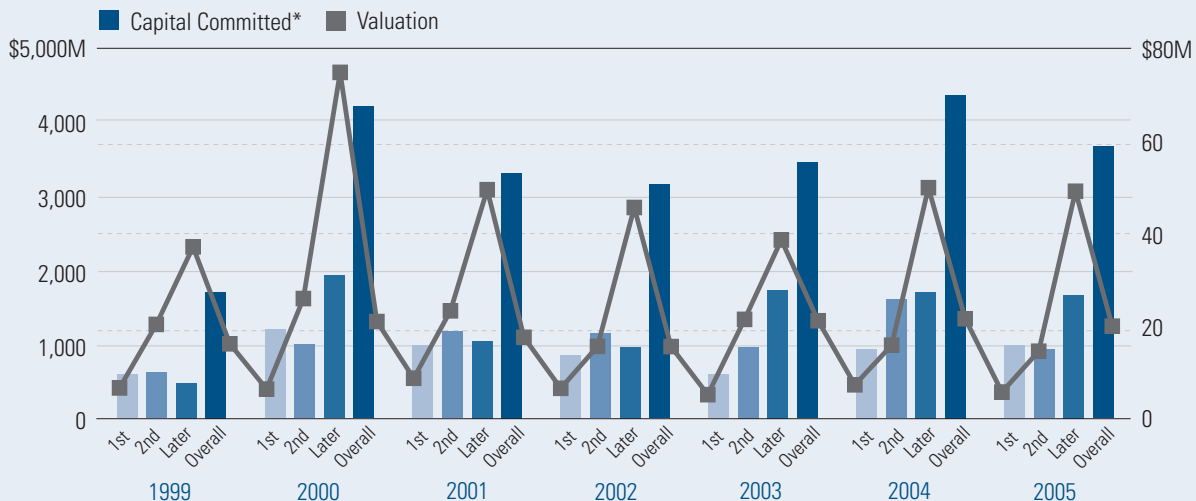
The two firms also were early backers of **XDx Inc.**, a developer of a molecular diagnostic to test the post-surgical rejection of heart transplants. The company closed on \$26.5 million in Series E financing in December.

For its part, the Denver-based ARCA, whose March Series A round was led by **Atlas Venture** and included the participation of **Boulder Ventures** and **Pequot Capital Management**, intends to resurrect a beta-blocker drug known as bucindolol that failed a broad-spectrum clinical trial, but that the company believes will be an effective treatment if given only to a subset of patients identified by genetic biomarkers. None of the firms had invested in Myogen.

First developed by Bristol-Myers Co. in the 1980s and by a trio of biotechnology companies in the 1990s, bucindolol was tested in over 4,000 patients, but failed a government-

Biopharmaceutical Valuations In Check

Biopharmaceutical investors continue to push for value. The post-money valuations of companies raising first and second rounds took a slight dip in 2005 from 2004. The drop occurred even as companies raising first rounds haven't raised that much capital since 2001. At the same time, annual commitments going to second rounds fell back in line after an extremely strong 2004. Later-stage valuations, meanwhile, also stayed relatively constant as did the number of dollars going into those rounds.



*Overall column includes any data from seed rounds or restarts. Source: VentureOne

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supported beta-blocker evaluation survival trial, more commonly known as the BEST trial. The drug was shelved as competing beta-blocker drugs received regulatory approval.

However, Bristow and others continued to study the BEST data and by analyzing the DNA make-up of participating patients, identified two genetic biomarkers associated with a subset of patients for whom bucindolol was most effective. Basically, the drug is more effective in non-African Americans.

Using the BEST data, which was pulled together over several years, ARCA now intends to submit a new drug application with the FDA towards the beginning of 2007 using those results coupled with the addition of its biomarker discovery. “We’re bringing on a full-bore regulatory staff right now,” Bristow said of ARCA’s expected additions to a staff of seven. Commercialization of the drug could come as early as 2008, Bristow said, with likely assistance from a sales and marketing partner.

Jean-Francois Formela, a senior partner at Atlas and a member of the ARCA board, described the existence of “compelling nuggets of data” within the BEST results, and commented that through the use of pharmacogenomics, the company is able to “leverage data that frankly was sitting there” in order to select patients who will benefit the most from bucindolol and remove the subset most likely subject to adverse effects.

Atlas’ experience in pharmacogenomics investing was one reason behind the firm’s investment in ARCA, according to both Formela and Bristow. The firm also was an early investor in now publicly traded Nitromed Inc. In June 2005, that company’s BiDil heart failure treatment was the first approved for a specific racial group, African Americans.

Biomarkers, which function as biological indicators for the identification, diagnosis and treatment of disease, are the key to personalized medicine. They are not always linked to race, which in many cases can be difficult to determine, but race is inherently the result of a polymorphism, variations in DNA sequence among individuals that can serve as biomarkers.

With the mapping of the human genome, the identification of these polymorphisms and genetic biomarkers presents the scientific community with opportunities to determine a patient’s – based on his or her genetic make-up – susceptibility to a disease and the effectiveness a given medication might have in treating that disease. Such is the case with bucindolol and with other personalized medicines; blockbusters such as Genentech Inc.’s Herceptin and Novartis AG’s Gleevec are among the examples from oncology. For example, there is a test associated with Herceptin that can determine which breast-cancer patients are likely to

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respond to the drug.

The FDA, led by Deputy Commissioner for Operations Janet Woodcock and Deputy Commissioner for Medical and Scientific Affairs Scott Gottlieb, has been public about its efforts to assist the advancement of personalized therapies. “The FDA’s commitment to pharmacogenetics and the advancement of this modality in terms of standard of care, we think is the right way forward for medicine,” Atlas Principal Bruce Booth said.

Through these efforts, the FDA continues to lend its support to the development of pharmacogenomics tools, specifically molecular diagnostics, or the use of DNA and RNA to identify a disease or a predisposition for a disease.

Molecular diagnostic companies of the CardioDx type may also be able to enter the drug development space through the use of a DNA bank to determine if a drug is better suited for only a specific population. “Now that most companies are storing DNA in their trials,” Formela said, “a molecular diagnostic company could say, ‘why don’t I take the DNA [of patients studied by someone else] and test it and see where the biomarker might lie.’”

Essentially, that is what ARCA did. Bristow said the use of the biomarkers with the data should double the efficacy of bucindolol, which should give it an advantage over existing beta-blockers on the market such as GlaxoSmithKline PLC’s Coreg and AstraZeneca PLC’s Toprol XL. In one comparison, Bristow suggested results of the bucindolol-biomarker combination are 20% better than Coreg’s results and 25% better than Toprol XL for the full patient (U.S. and non-U.S.) populations. Meanwhile, results from U.S. data alone suggest ARCA’s beta-blocker is two to three times more effective than Toprol, with mortality rates significantly reduced.

The gamble is that the FDA will see any increased response rate and targeted therapies as an advantage and that physicians feel it will improve patient outcomes and, perhaps, practice management.

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