

# WILL BIOTECHNOLOGY KEEP THE HEART HEALTHY?

Coronary heart disease kills more Americans each year than any other disease. So why have biotechs lagged in developing treatments? No quick answers, but change is coming. **BY KATHERINE T. ADAMS**, *Senior Editor*

**W**hen the question was posed to Christopher J. Reinhard, chairman and CEO of San Diego-based Cardium Therapeutics, as to why biotech companies have focused their efforts on treating cancer and degenerative diseases instead of the illness that kills most Americans — coronary heart disease (CHD) — his response was swift. “You’re talking to the guy who has spent the last 10 years of his life working on drugs in this area. I have the same question myself.”

Cardium is one of a handful of mainly small biotech companies developing and testing new therapies, like angiogenesis stimulators, that target heart disease pathways.

“In 1995, when we saw the angiogenic response and improved function obtainable using a fibroblast growth factor gene [a gene that induces cellular functions], it was clear there was inherent capacity for an injured heart to heal itself from within when a biologic sets that natural healing process in motion,” Reinhard says. He was so im-

**“The heart is a unique organ. It has an innate biological capacity to remodel itself, based on changed circumstances,”** says Christopher J. Reinhard, chairman and CEO of Cardium Therapeutics. **“So we are leveraging the heart’s ability to remodel itself.”**

PHOTOGRAPH BY ROBERT BURROUGHS



pressed that he has been working exclusively on cardiovascular products since 1996 — “11 years now, but everyone says it happened overnight.”

There’s always great enthusiasm when an idea first hits, Reinhard says, “Then commercial reality sinks in, because we are dealing with complex systems that have evolved over millions of years.” Reinhard points to a recent article in the *Harvard Business Review*<sup>1</sup> that says every drug is a one-of-a-kind drug, because an incredible amount of know-how, dedicated skill, and intuition about the drug — not to mention time — is needed for each.

The heart has the innate biological capacity to remodel itself, which is what turned Cardium on to the idea of cardiac plasticity. For one thing, Reinhard explains, the heart has the ability to grow additional blood vessels. “The body does, too, but the heart does it very specifically in people with coronary artery disease.”

Cardium is recruiting for a phase 3, randomized, placebo-controlled, double-blind trial called AWARE (Angiogenesis in Women with Angina pectoris who are not candidates for Revascularization) to test its key product, Generx (alferminegene tadenovec, Ad5FGF-4), a non-surgical angiogenic gene therapy for treating chronic angina due to coronary artery disease.<sup>2</sup> Basically a deactivated cold virus that has the growth factor gene spliced into it,

<sup>1</sup>Collis, D, Smith T. Strategy in the 21st Century Pharmaceutical Industry: Merck & Co. and Pfizer Inc. Nov. 27, 2006.

<sup>2</sup>Generx received fast-track status from the FDA on July 18.

Generx is a one-time infusion into the heart, where it promotes and enhances angiogenesis. A standard diagnostic catheter — the same that is used for an angiogram — is used to administer the drug. “It was originally designed to be done at the time of the angiogram, so it’s very

**“Understanding the genetic variations [in heart disease] is going to require a more collaborative approach, particularly at the preclinical level, for drug development.”**

— ROBERT GOLDBERG, PHD  
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simple, which is one of the beauties of it,” Reinhard says.

Generx has a binding affinity to the Cocksackie adenovirus receptors (CARs) in the heart. In preclinical studies, it stayed in the heart, which Reinhard says was a surprise finding: “When you infuse it deep down into the coronary arteries, it has a very high level of first-pass cardiac uptake.” The drug is intended for patients who have had bypass surgery or drug-eluting stents and still have angina despite taking maximum medication.

Following clinical studies that have already involved more than 650 patients, Cardium believes a one-time infusion of its angiogenic gene therapy is capable of dramatic improvements in coronary blood flow even in patients with severe heart disease. Having the biologic targeted to the heart and produced there for a sustained period are both seen as critical to that process.

Jack Jacobs, PhD, chief scientific officer at CardioVascular BioTherapeutics (CVBT), based in Las Vegas, also wonders why it has taken so long to develop cardiobiologic agents, but theorizes that effective delivery of a drug to the heart has been problematic.

“Protein growth factors were tried 10 years ago,” Jacobs says. Biologic manufacturers like Amgen and Chiron, which were attempting to develop cardiobiologics, injected the growth factors into the coronary arteries, “which is logical,” Jacobs says, “but if you think about it, once you get something into the arteries it gets swept out pretty quickly. What we’re finding

is that you really have to put the growth factor into the heart muscle to get a good response.”

Growth factors need to stay in the heart long enough to get vessels that are large enough to carry enough blood to make a difference, Jacobs says. Some growth factors only cause sprouting of capillaries, but others can progress to the small artery stage so that they carry enough blood “where you can get some real relief of symptoms.”

The intent of angiogenesis treatments is to mimic a natural process in which the body responds to a diminished blood supply to vital tissues and organs, explains Jacobs. This is in contrast to the treatment of many cancers, where antiangiogenesis therapies are used to block new vessel growth and starve tumors.

Although several options are available to clear blocked arteries, such as coronary artery bypass graft, percutaneous transluminal



PHOTOGRAPH BY JEFF GREEN

**Angiogenic therapy** is a proven safe method of stimulating the natural process of new blood vessel formation, says Jack Jacobs, PhD, chief scientific officer at CardioVascular BioTherapeutics. “It’s a treatment option that can be offered early in the [cardiac] disease process to complement other forms of treatment.”

coronary angioplasty, and the use of stents, all have various drawbacks and are not always effective over the long term. Jacobs also refers to the so-called “no option” patients — usually women — who have microvascular disease, for which no therapy exists, or who suffer from cardiac ischemia and are not candidates for surgical intervention. These are people for whom angiogenesis may be an option.

CVBT plans to initiate a phase 2 clinical trial of its fibroblast growth factor FGF-1 drug, CVBT-141A, late this year.

### NOT A SINGLE DISEASE

CHD, cardiovascular disease (CVD), and coronary artery disease,

terms often used interchangeably, don’t just happen to strike an individual. They are the result of a process that can start as early as childhood and continues, often silently, into middle age and beyond. Genetic factors and predisposition to heart disease, vascular defects, and a host of environmental risk factors, such as diet, smoking, and stress, play major roles. Current theory holds that atherosclerosis is the prime factor in heart ailments, stroke, and fatal heart attacks, but other theories are quickly emerging to suggest that inflammation of the immune system and even viruses and bacteria may cause heart disease. Reinhard and others see heart disease as a relatively new

phenomenon in human evolution, driven by increasing industrialization and our ability to live 60, 70 years, or longer: “Because it typically arises later in life — after child-bearing years — probably there has been relatively little selective survival pressure in our species to deal with coronary artery disease.”

Like cancer, heart disease has multiple forms and is closely linked to a number of comorbidities, such as hypertension, diabetes, and degenerative diseases, each of which can cause or exacerbate heart disease. But unlike many cancers, heart disease can be prevented or controlled. So the question arises as to which facet of heart disease should the biotechs focus on first?

Ralph J. Zitnik, MD, vice president of development at Nuvelo, headquartered in San Carlos, Calif., says it's hard to bundle all cardiovascular diseases into one package. Increasingly, inflammation is viewed as an important mechanism that drives plaque rupture, Zitnik says, "but I would say that we are focused on opportunities that target acute care and answer unmet medical conditions regardless of mechanism." For now, the company is looking at patients who have suffered or are suffering one of the sequela of underlying CVD, like a heart attack, stroke, peripheral vascular occlusion, or who need bypass surgery or percutaneous coronary intervention. "Our focus is later in the natural history of a patient's disease than some other companies are targeting."

Nuvelo is developing three different drugs — each based on a different technology — including alfineprase, a thrombolytic agent for acute ischemic stroke, catheter occlusion, and acute peripheral arterial occlusion.<sup>3</sup>

Alfineprase has a mechanism of action that is different from the typical clot busters, Zitnik says, "directly lysing clots rather than acting indirectly as a plasminogen activator." Alfineprase is a one-shot drug given in response to an acute clinical event, such as peripheral arterial occlusion. The drug is infused through a catheter that is passed into or next to the clot. It lyses the clot, opens the artery, and then is

<sup>3</sup>Nuvelo plans to reinitiate SONOMA-3 (Speedy Opening of Non-functional and Occluded catheters with Mini-dose Alfineprase), a phase 3 trial, later this year. Development had been suspended after the agent did not meet primary endpoints in another phase 3 trial last year.

inactivated by a circulating blood protein called alpha-2 macroglobulin (A2M).

Another Nuvelo product in development, recombinant nematode anticoagulant protein c2 (rNAPc2), inhibits thrombin's ability to generate fibrin, the protein that provides the scaffolding for blood clots. "It's actually a recombinant protein similar to one that occurs in *Ascaris*, a parasitic worm," Zitnik says, and inhibits the factor X/factor VIIa/tissue factor complex — the critical first-step enzyme in the coagulation cascade. rNAPc2 is given acutely, as an intravenous infusion, although Zitnik says it might end up as a subcutaneous drug. In the small studies Nuvelo has done so far, the drug was given in response to a deep venous thrombosis or an acute coronary syndrome.

Results of Nuvelo's ANTHEM<sup>4</sup> acute coronary syndrome study, published by Guigliano this year in the *Journal of American College of Cardiology*, showed that the drug could achieve adequate suppression of thrombin generation to stop ischemia, as measured by electrocardiograms. "These findings are a good predictor of clinical outcomes, but larger studies are necessary to draw any conclusions," Zitnik says. "Still, what we have seen in the ANTHEM study has us hoping this drug could find its way into treatment for this kind of situation."

Aptamers, like Nuvelo's NU172, also show promise for use in heart disease. Zitnik hopes NU172 can be used to perform bypass surgery more quickly and safely than low-molecular-weight heparin and other anticoagulants that are used today.

<sup>4</sup>Anticoagulation with rNAPc2 to Help Eliminate MACE.

"We have set a goal to try this year or early next to get the drug into patients in a first-in-human study."

And what about cost?

"Our drugs are given in a relatively limited number of doses in the event of an acute and catastrophic event," says Zitnik. "Clearly, the talk today is about the fourth hurdle, where it's not only efficacy, safety, and product quality that we have to demonstrate, but also value in the perspective of a third-party payer — decreases in hospital stay and disability, for example. In recent years, demonstrating these attributes in studies has become an increasingly important goal of all drug development programs, but especially in cardiovascular disorders."

## HURDLES TO OVERCOME

Ernst & Young, in its 2007 Global Biotechnology Report, "Beyond Borders," says biotechnology is a classic example of a disruptive technology — a breakthrough technological innovation that displaces the dominant existing technology. Big pharma initially dismissed the significance of large-molecule drugs and biotech innovations, but by 2006 the disruptive process was complete — and today, large mainstream pharmaceutical companies compete aggressively either to acquire or to partner with companies thought to offer the next generation of biotech platforms and technologies.

Recent partnerships or collaborations, like AstraZeneca and AtheroGenics, Bristol-Myers Squibb and Isis Pharmaceuticals, Cyokinetics and Amgen, and Genzyme and Medtronic, would seem to confirm that's what's happening in the cardiobiologics field.

<b>RECENT RUNS, HITS, AND ERRORS</b>					
<i>Selected biologic and targeted cardiovascular agents not mentioned in this article</i>					
<b>Agent (trade name)</b>	<b>Manufacturer</b>	<b>Indication</b>	<b>Mechanism of action</b>	<b>Route of delivery</b>	<b>Status</b>
<b>Across the plate</b>					
Ambrisentan (Letairis)	Gilead Sciences	Pulmonary arterial hypertension	Endothelin receptor antagonist	Oral	Approved June 2007
Fondaparinux sodium (Aixtra)	GlaxoSmith-Kline	Unstable angina and non-ST segment elevation myocardial infarction	Anticoagulant	Injection	Approved March 2007
<b>Rounding third</b>					
Nebivolol	Mylan/Forest Laboratories	Hypertension	Beta-1 receptor blocker	Oral	New drug application in review
<b>On the basepaths</b>					
Vernakalant hydrochloride IV	Cardiome/Astellas Pharma US	Post-operative atrial fibrillation	Ion channel blocker	Intravenous	Phase 3 (ACT 2) trial completed June 2007; ACT 4 open-label safety study ongoing
Lixivaptan	Biogen Idec/Cardiokine	Hyponatremia	Vasopressin antagonist	Oral	Phase 3 trial late 2007
BAY 59-7939 (Rivaroxaban)	Bayer	Anticoagulant	Direct thrombin inhibitor	Oral	Phase 2 trial completed
DG051	deCode Genetics	Acute myocardial infarction	Leukotriene A4 hydrolase inhibitor	Oral	Phase 2 trial late 2007
DG041	deCode Genetics	Arterial thrombosis	Antiplatelet/EP3 receptor antagonist	Oral	Phase 2a studies completed June 2007
<b>Out at the plate</b>					
Sitaxsentan (Thelin)	Encysive Pharmaceuticals	Pulmonary arterial hypertension	Endothelin receptor antagonist	Oral	Approval denied June 2007 (FDA issued third approvable letter)
SOURCE: BIOTECHNOLOGY HEALTHCARE ANALYSIS					

But few efforts have been successful. An example is CV Therapeutics' regadenoson (Ranexa), a molecular anti-angina drug and the first new approach to treat chronic

angina since the early 1980s. Regadenoson was developed in partnership with Astellas Pharma US, and although it recently failed to meet an efficacy endpoint in a sec-

ond phase 3 clinical study, CV still expects to get FDA approval of the drug. Pfizer's torcetrapib, a protein inhibitor to treat elevated cholesterol levels, also received a well-

publicized death blow when safety considerations ended phase 3 trials. Development of torcetrapib began 17 years ago, and its history underscores the difficulties that CVD biologics face. AstraZeneca and AtheroGenics' plaque reducer, AGI-1067, also failed to show efficacy in the phase 3 ARISE<sup>5</sup> trial.

"Don't put too much of a gloss on these things," says Robert Goldberg, PhD, vice president for the New York-based Center for Medicine in the Public Interest (CMPI) and who keeps a close eye on biotech developments. Most clinical trials aren't conducive to measuring the effectiveness of targeted therapeutics in some populations, Goldberg says. "The blockbuster model prevails."

Similarly, Goldberg suggests, a dearth of scientific know-how still guides regulatory and clinical practice patterns. "The FDA is not really up to speed scientifically on the techniques that could be used to treat CHD," he says. Further, Goldberg maintains, cardiologists still treat cardiovascular diseases on a one-size-fits-all basis — like trying to reduce blood pressure or cholesterol levels, which then become surrogate endpoints for treatment standards and clinical trial development.

Cancer provides a very good model of how the cardiovascular situation is progressing, says Goldberg, who points to Michael A. Weber, MD, a professor of medicine at SUNY–New York and a pioneer in treating prehypertension. Weber, who also is the chairman of CMPI, has found that even at the phenotypic level there are substantial variations in treating hypertension

<sup>5</sup>Aggressive Reduction of Inflammation Stops Events.

with small-molecule drugs. That will be the case to an even greater degree with biologics, Goldberg says, "So, if CVD follows form, you will see that toxicities will vary by polymorphisms."

Based in part on his experience as chairman of a U.S. Food and Drug Administration reform task force a couple of years ago, Goldberg predicts that many biologics will wind up being used in a similar fashion as cancer drugs — that is, as targeted therapies. Some biotechs are now looking at the technology of epigenetics (cell therapies) to get a "snapshot" of what actually is happening in patients as heart disease progresses. And then, there is the stem cell research arena (See BIOTECHNOLOGY HEALTHCARE, June 2007). "So the field of heart disease treatment is undergoing intensive investigation right now," he says.

How many times, though, can you inject or infuse a biologic into the heart or arteries? That's the challenge that biotechs faced with targeted therapies for cancer. Take imatinib (Gleevec), says Goldberg.

"The initial formulation was an injectable, but the folks at Novartis said, 'Well, if this is going to have to be taken over a lifetime, there's no way you will want to send someone to an infusion center for that long.' So they reformulated it into a small molecule."

### MODEL FOR SUCCESS?

Biotechs looking for breakthroughs in cardiovascular care have faced numerous challenges, running into dead ends and unexpected findings. How to move drug development along more quickly?

One way, Goldberg says, would be for researchers to be more col-

laborative in the preclinical stages, and to work closely with the FDA to come up with a more predictive approach to the design of clinical trials. That would require using adaptive trial designs and data analysis — effectively skipping the translational issue. Much more information, then, would come out of the prediscovery phase.

He also puts the onus on the FDA to develop better standards for evaluating cardiobiologics and to get involved in the drug development process earlier. That way, the effects of these therapies can be measured more accurately in only the most appropriate candidates — ultimately reducing the time and cost of bringing a product to market. The development of a pharmacogenomic test to market alongside the product could make a non-blockbuster drug that works in the vast majority of a subset of patients just as valuable — maybe even more so in the eyes of third-party payers — than a blockbuster that works in only 30 to 50 percent of those to whom it is prescribed.

For all the effort to bring cardiobiologics to market (see Table), the potential of many of them to act as targeted therapies leads Goldberg to believe that they would be better used on a preventive basis. Consider prevention of left ventricular failure, a highly prevalent problem. "You could save the health system billions of dollars, save lots of lives, and do something noninvasive," he says. "If you could find a precursor for that — a genetic analysis or test — then you would be way ahead of the game."

It's a game that is far from over, but the winners are sure to be richly rewarded. **BH**