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Emerging Medical Ventures

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ALL PROFILES ISSUE

BIOTECHNOLOGY

Cardioxyl Pharmaceuticals

Treating acute decompensated heart failure

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Contact: Christopher A. Kroeger, MD, President & CEO
Business: Nitroxyl chemistry platform for cardiovascular drug development
Founded: November 2005
Founders: David Kass, MD (Johns Hopkins University Medical Institutions [JHMI]); Nazareno Paolocci, MD, PhD (JHMI); John Toscano, PhD (JHMI)
Employees: 5
Financing to Date: $14.5 million
Investors: New Enterprise Associates Inc.; The Aurora Funds
Board of Directors: James Barrett, PhD (New Enterprise Associates); Jeff Clark (The Aurora Funds); Robert Garland, MD (New Enterprise Associates); Charles Sanders, MD (Institute of Medicine of the National Academy of Sciences, CSIS Board of Trustees, Project HOPE, Foundation for the National Institutes of Health, UNC Health Care System); Christopher A. Kroeger
Clinical Advisory Board: Wilson S. Colucci, MD, FACC, FAHA, Chairman (Boston University Medical Center); William T. Abraham, MD, FACP, FACC (Ohio State University College of Medicine); Michael Givertz, MD (Harvard Medical School); David Kass; Marvin Konstam, MD (Tufts University School of Medicine); Doug Mann, MD (Washington University School of Medicine, Barnes Jewish Hospital); Ralph Snyderman, MD (Duke University School of Medicine); James Young, MD (Case Western Reserve University)

Nitric oxide (NO). It has garnered much attention for its vasodilating effects, which ease the load on the heart. Therapies such as nitroglycerine and amyl nitrate act as NO donors.

That success attracted attention to its chemical cousin, nitroxyl (HNO), which got its start at the end of the 19th century with Angeli's Salt, a compound that spontaneously produces nitroxyl under certain conditions. Nitroxyl remained in obscurity throughout much of the 20th century. But when researchers began to demonstrate nitric oxide's potential as a cardiovascular therapy, nitroxyl gained renewed attention because of its chemical similarity, although experiments showed that there is no chemical conversion between the two species and they have different physiological effects.

It was a research coincidence that brought nitroxyl to the attention of David Kass, a professor of cardiology at the **Johns Hopkins University School of Medicine**, and Nazareno Paolocci, a post-doc in his lab. At the time, they were conducting basic preclinical investigations of cardiac function, ventricular-arterial interaction, vascular stiffening and mechanosignaling. A colleague at the **National Institutes of Health's National Cancer Institute** began to work with Angeli's Salt for another indication and knew that nitroxyl could have effects on the cardiovascular system, so he asked Kass and Paolocci to test some of their compounds to be sure there were no important side effects.

They found that Angeli's Salt produced improvements in contractility in normal canine models and, subsequently, in heart failure canine models. Both models demonstrated significant improvements not only in contractility, but also in lusitropy (relaxation) and cardiac loads with no signs of arrhythmogenic potential. "It was quite by luck that they originally got involved," says Chris Kroeger, president and CEO of **Cardioxyl Pharmaceuticals Inc.**

When those effects had been demonstrated, Kass co-founded Cardioxyl in 2005. The following year, it raised a $14.5 million Series A round from New Enterprise Associates and The Aurora Funds.

Angeli's Salt is not suitable for use as a drug, so the company embarked on a medicinal chemistry program to develop nitroxyl donors with better properties.

The company's lead compound is CXL-1020. Other compounds are in earlier stages of development. CXL-1020 produces a suite of effects; it improves the heart's ability to squeeze and its ability to relax and refill, while also acting on the peripheral vasculature, causing dilation and thus reducing load.

The mechanisms haven't been fully defined, but researchers do know that the contractility and relaxation effects are related to calcium ion handling in heart cells (myocytes). Calcium ions enter the cell and trigger the release of much higher levels of calcium from intracellular organelles. That calcium enters the cytoplasm and ultimately causes the myocyte to contract. Nitroxyl interacts with both the ryanodine receptor and SERCa 2a, both of which are involved in calcium cycling within the myocyte

"Nitroxyl enhances the efficiency of calcium cycling in the myocyte without dramatically effecting the overall calcium load or the influx of calcium from the extracellular space, (and that leads to) more effective myocardial contraction and relaxation," says Kroeger.

The vascular dilation in the periphery is less well understood, but it must operate through a different mechanism because peripheral smooth muscles lack the calcium channels found in myocytes.

The company chose to target acute decompensated heart failure (ADHF) in its clinical program, in part because preclinical data suggested it and in part because nitroxyl is short-lived once it is released, making it a more natural fit for an acute condition.

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ADHF occurs in patients with chronic heart failure who experience some event—a salty meal, perhaps, or a failure to take medicine–that causes the patient to arrive at a new equilibrium, where the heart doesn't have enough reserve to meet the body's needs. "They go from a stable but somewhat brittle state to acutely decompensated. Fluid backs up; they have lung edema; they're short of breath," says Kroeger.

Physicians generally focus on reducing the fluid buildup with diuretics to relieve edema. Nitrates can be used as peripheral vasodilators to expand vasculature volume and increase flow.

Physicians have few other options, Kroeger says. The drug nesiritide (*Natrecor*, marketed by **Johnson & Johnson**) dilates blood vessels but has run into issues with renal toxicity, though it remains on the market. However, it has little primary effect on the heart. Another class of drugs called inotropes affects heart contractility, but those drugs are usually used only in very sick patients because of their association with ventricular arrhythmias and increased mortality.

All of the existing drugs work on the cyclic AMP pathway. Cardioxyl's drug is unique mechanistically. "It doesn't lead to calcium overload, which the inotropes do, and we think that as a consequence we won't produce arrhythmias," says Kroeger.

Other companies working in the space include **Nile Therapeutics Inc.**, **Cytokinetics Inc.**, **Merck & Co. Inc.**, and **Sigma-Tau SPA**. "Most of the competition is in the vasodilator or diuretic class, just working on load. They're not really affecting the whole spectrum. We've not seen another drug that demonstrates this full suite of effects, and nobody else is developing a nitroxyl drug that we know of," says Kroeger.

The market is significant. There are over a million hospital admissions each year for ADHF in the US alone, and around 22 million patients with heart failure worldwide. Kroeger anticipates a market in the $750 million to $1 billion range. "If it's a non-toxic drug that demonstrates that full suite of physiological effects (on the heart and peripheral vessels), it could reasonably move to a first-line therapy," says Kroeger.

This Spring, the company initiated a Phase I/IIa clinical trial of CXL-1020. Kroeger won't predict when the drug might receive FDA approval. He doesn't expect any severe regulatory hurdles, but he does think that the bar for efficacy is rising. "Neseritide was approved on hemodynamic measures, but it's clear that won't be sufficient for approval in the future. We need to show hemodynamics to give credibility to our data, but the ultimate end points are symptomatic improvement, hospital admission rates, and short-term mortality."

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—Jim Kling