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BIOTECHNOLOGY

NormOxys Inc.

Enhancing tissue oxygen levels for clinical benefit

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Contact: Martin Tolar, MD, PhD, President & CEO
Business: Oxygen-enhancing therapeutics
Founded: April 2004
Founders: Claude Nicolau, PhD, CSO; Jean-Marie Lehn, PhD, Conrad J. Bletzer, Jr.
Employees: 12
Financing to Date: $30 million
Investors: Index Ventures; Care Capital
Board of Directors: Jean-Pierre Garnier, PhD (formerly GlaxoSmithKline); Martin Tolar; Claude Nicolau; Francesco DeRubertis, PhD (Index Ventures); Michele Ollier, MD (Index Ventures); Argeris Karabelas (Care Capital); Board Observer: Conrad J. Bletzer, Jr.
Scientific Advisory Board: Jean-Marie Lehn (University of Strasbourg); Wilson Colucci, MD (Boston University Medical Center); John Cooke, MD, PhD (Stanford Cardiovascular Institutes); Mark Creager, MD (Brigham and Women's Hospital); Barry Massie, MD (University of California at San Francisco); Michael B. Atkins, MD (Beth Israel Deaconess Medical Center), Marc B. Garnick, MD (Beth Israel Deaconess Medical Center); Keith Stuart, MD (Lahey Clinical Medical Center), Claude Nicolau

Deep thinking about nature has long inspired scientific achievement. Centuries after Leonardo daVinci sketched a plan for a helicopter after musing on a dragonfly, the founders of **NormOxys Inc.** are working to commercialize molecules similar to those that give migratory birds the fortitude to fly thousands of miles.

Claude Nicolau, a co-founder of the company and its CSO, learned as a graduate student of the fascinating discovery made by Benesch and Benesch in the late 1960s. The pair of scientists found that migratory birds have in their blood a substance that allows them to utilize more of the oxygen carried by hemoglobin molecules than most creatures do. When this compound, inositol pentaphosphate, binds to the protein hemoglobin, its presence helps release up to three of the four oxygen molecules that hemoglobin picks up in the lungs and carries out to the body. In humans, only a single molecule of oxygen is off-loaded. Because this compound exerts its influence on oxygen by binding to a different site, versus interacting directly with it, it is considered an "allosteric [other site] modulator."

> If OXY111A is ultimately approved as a drug, it will be the first known as capable of increasing the off-loading of oxygen from hemoglobin.

Nicolau says he has spent 20 years studying allosteric modulators and pondering how to apply understanding of the birds' special chemistry to human medicine. The molecule isolated from birds, and close analogs, turned out to be unsuitable as drug candidates, in part because they could not enter the erythrocytes that contain hemoglobin in the human body. To crack the problem, Nicolau asked Nobel Laureate Jean-Marie Lehn, who is director of the laboratory of supramolecular chemistry at the University of Strasbourg and a chemistry professor at the College de France in Paris, to help identify a novel allosteric effector of hemoglobin that would be capable of entering red blood cells and non-toxic. Lehn, who co-founded with Nicolau Alantos Pharmaceuticals Inc. (now part of **Amgen Inc.**) and **AC Immune SA**, became a co-founder of NormOxys when he identified OXY111A, inositol hexaphosphate, which combines transporter-binding ability with the key ability to attach allosterically to hemoglobin.

NormOxys is betting that OXY111A can help elevate oxygen levels in human tissues that lack it, and so become a treatment for a range of disorders, from chronic heart failure (CHF) to diabetic retinopathy, traumatic blood loss and even cancer. A Phase I clinical trial in healthy volunteers began in late May 2010, in preparation for a trial against an unnamed form of cancer. The company will use the trial not only to test safety but to investigate the compound's pharmacological profile. If OXY111A is ultimately approved as a drug, it will be the first known as capable of increasing the off-loading of oxygen from hemoglobin. NormOxys has dubbed OXY111A and related compounds "oxyrens," short for oxygen-release enhancers.

NormOxys is by no means the first company to attempt development of molecules intended to provide oxygen to tissues in need of it. Several oxygen transporters intended as "blood substitutes" have failed because of unacceptable side effects, among them **Biopure Corp.**'s *Hemopure*, **Northfield Laboratories Inc.**'s *PolyHeme* , and **Baxter Healthcare Corp.**'s *HemAssist*.

OXY111A has better odds for success, contends NormOxys President and CEO Martin Tolar, because the compound enhances a mechanism already fundamental to the body: transporting oxygen via hemoglobin. "Our compound only oxygenates hypoxic tissues," he declares, noting that the firm has conducted a number of studies to confirm this is so. Normal cells are damaged by influx of excessive oxygen.

Tolar himself, who joined NormOxys in June 2009, may boost the start-up's chances for success by dint of the scientific and business acumen he brings. As EVP and chief business officer for CoMentis Inc., Tolar orchestrated a high-value deal bringing the big Japanese drugmaker **Astellas Pharma Inc.** access to that biotech company's beta-secretase-based platform for Alzheimer's disease treatments. The alliance struck in 2008 earned CoMentis $100 million up front and $660 million in downstream milestones. Previously, Tolar held senior strategic and clinical positions at Pfizer Inc., including leading the neuroscience licensing team, which under him finalized several large deals.

NormOxys has decided on heart failure as the initial indication for OXY111A, because CHF is a disease that is purely oxygen-dependent. Clinical success there would support the company's explanation of its compound's mechanism of action as well as satisfy unmet medical need. CHF often follows severe heart attacks, when damage to the vital organ (caused by suddenly interrupted blood flow) reduces the heart's ability to pump and to oxygenate itself and other tissues. As the disease progresses, the heart muscle expands, and this remodelling further weakens the contractions necessary to pump blood out to the body "Late-stage CHF patients can barely walk," Tolar points out, noting that at such point, even minimal exercise can cause the heart to decompensate.

Current approved treatments for CHF, such as beta-blockers and ACE inhibitors, generally improve patients' exercise capacity by just 5 to 10%, Tolar says: "Most medicines prescribed for CHF work by improving contractility, but they are not solving the problem of the heart's need for oxygen." OXY111A might do better. In well-accepted mouse models of the disease, the compound improved exercise capacity by a remarkable 70%. Improving oxygen supply not only makes the heart pump better, Tolar declares, but may actually be able to reverse remodeling. In animal-model studies over six months, he says NormOxys has "shown we can stop remodeling of the heart." The company plans to test its candidate in combination with existing therapies, knowing that clinicians are unlikely to switch CHF patients off the only drugs known to benefit the condition.

Tolar figures there is "very little translational risk" in developing OXY111A for a cardiovascular disease like CHF, but explains that NormOxys also intends to develop the compound as a treatment for cancer, because "the data are so dramatic, we feel we must pursue this." Tolar concedes that experienced pharmaceutical executives and clinicians alike were initially skeptical of the idea that improving oxygenation of cancerous tissue would be beneficial. If anything, they suspected the boost might spur tumor growth. That line of thinking mirrors current clinical practice in oncology, where anti-angiogenic compounds are administered in hopes of depriving tumors of nutrients and oxygen by shutting down blood vessel formation.

NormOxys is emboldened by growing stacks of evidence that indicate tumors respond to hypoxia by activating a molecular pathway that increases production of a protein called hypoxia-inducible factor-1 alpha. HIF-1a is now known to promote angiogenesis, and also to stimulate production of specific cell structures that let cancer cells pump out anti-cancer drugs. Researchers are sadly realizing that the very drugs meant to kill tumors are in some cases inducing cellular changes that allow the cancer cells to become drug-resistant.

"It turns out that 70 to 80% of tumors are dependent on this hypoxia-induced pathway," Tolar explains. He points out that HIF-1a is produced "upstream" in the same molecular pathway that further downstream includes genes for proteins such as VEGF (vascular endothelial growth factor), EGF and others known to promote tissue growth. There are effective drugs now on the market that target only VEGF, Tolar notes, and this knowledge makes him and NormOxys willing to bet that OXY111A could prove to be an even more potent treatment for cancer because it would act further upstream.

"The beauty of this approach is that it is not the typical way of treating cancer," Tolar declares, adding, "Here, you'd be supporting some of the homeostatic mechanisms for clearing out cancer." Studies by numerous researchers are showing that inhibiting HIF-1a can activate apoptosis and promote immune surveillance, he notes. The data NormOxys are generating suggest that normalizing oxygen levels normalizes pressure in the core of the tumor, and not only takes away stimuli for cancer growth but also increases protective factors. "This is not just conjecture," Tolar asserts: "We do have experimental evidence" that includes documented effects of OXY111A on levels of VEGF and apoptotic markers as well as imaging of vessels.

Early studies in animal models of cancer, initiated by Nicolau and Lehn are producing data every bit as impressive as those for CHF, Tolar emphasizes. "We are seeing dramatic results in cancers where you never see resolution," he declares: "Over and over, with melanoma, hepatoma, pancreatic and colon cancers, we are seeing that after treating the cancer with OXY111A for six to eight weeks it goes away and does not come back." That happy outcome is reportedly not being replicated in the company's comparison studies involving VEGF inhibitor alone and combinations of conventional chemotherapeutics.

The strong preclinical results NormOxys is documenting are rousing interest from formerly skeptical pharmaceutical executives and even prompting requests for compassionate use that the company simply cannot grant at this early stage, Tolar says. The data and the inquiries enabled the company to announce a Series B financing of $17.5 million on May 24, bringing its total financing to date to approximately $30 million. NormOxys likely could have raised more money, given the strength of its scientific, clinical and business connections, but this amount should support proof-of-concept studies of OXY111A in both CHF and cancer, without being overly dilutive.

NormOxys intends to seek a partner or partners to advance its work on oxyrens, preferring a single partner that will appreciate the value of the entire platform over an entity that would wish access to OXY111A for just one disease area or the other.

In the recently announced Series B financing, initial backer Index Ventures was joined by Care Capital, whose partner Argeris "Jerry" Karabelas joined the NormOxys board of directors.

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— Deborah Erickson