

# “The Pink Sheet” DAILY

## PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

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### Privately-held NormOxys Raises \$17.5 Million Series B To Further Develop Its Novel “Oxyren” Program

NormOxys, which is developing small molecule oxygen-enhancing drugs to treat a variety of diseases, announced May 24 a \$17.5 million Series B financing. In addition to existing backer Index Ventures, Care Capital participated in the most recent financing round, with partner Argeris “Jerry” Karabelas joining the start-up’s board of directors.

NormOxys’ strategy is fairly representative of a subset of biotech start-ups with novel platform technology complemented by A-list backers and a top-notch scientific pedigree. By raising a sizeable but not extraordinary amount of additional cash, the company avoids too much dilution and can aim for a more lucrative big pharma partnership - whether it’s a licensing deal or acquisition - once the lead molecule, and thus the company’s platform, have been derisked.

And Martin Tolar, the company’s CEO, is aiming high. “We could absolutely do a deal right now if we wanted to,” he said in an interview. “But why do a deal now and cap what we can get when we are well funded?” Indeed, with more than \$30 million in total funding, Tolar insists NormOxys is well positioned to take its lead product, OXY111A, through proof-of-concept clinical trials in two different disease settings, congestive heart failure and cancer.

Tolar has engineered significant deals before. The former EVP and chief business officer for CoMentis, Tolar partnered that biotech’s beta-secretase platform for Alzheimer’s disease with Astellas in a 2008 alliance worth \$100 million upfront and \$660 million in downstream milestones.

OXY111A, dubbed an “oxyren” for its oxygen-releasing capabilities, is a novel small molecule capable of altering the activity of hemoglobin, the protein in red blood cells responsible for ferrying oxygen to the body’s tissues. In the oxygen-rich environment of the lung, hemoglobin is fully loaded with a payload of four oxygen molecules. As it travels to the body’s tissues, hemoglobin offloads a single molecule of its oxygen shipment. Oxyrens bind to hemoglobin at a site distinct from the oxygen binding site. This so-called allosteric modulation tweaks the hemoglobin in such a way that it releases two oxygen molecules to hypoxic tissue instead of one - doubling the amount of gas delivered at any one time.

“Our technology attempts to recapitulate the natural process” said Tolar. The difference is “our compound changes the offloading capacity of hemoglobin” so that more can be delivered to tissues where it is needed, he said. That’s important because it shouldn’t result in excess oxygen delivery to normal tissue, which because of free radical production, can cause damage.

Equally important, says Tolar, is the fact that the molecule triggering the actual physiological changes is oxygen itself, not the oxyren. Thus, potential off-target side-effects that have scuppered artificial blood substitutes such as Biopure’s *Hemopure*, Northfield Laboratories’ *PolyHeme*, and Baxter Healthcare’s *HemAssist*, should be less problematic.

Certainly, the preclinical data have been impressive. Studies in mice show that OXY111A can increase exercise capacity by roughly 70 percent. If the molecule has the same impact in humans, Care Capital’s

Karabelas believes it will be a "breakthrough biological technology." Certainly it would far exceed the 5 percent to 10 percent increase in exercise capacity standard therapies such as beta-blockers and ACE inhibitors currently provide congestive heart failure patients.

### **Elegant solution masks difficult chemistry**

Karabelas recalled the first time he saw NormOxys's preclinical data. "There was an 'aha' moment and you immediately wondered why someone hasn't done this before," he said. But it turns out designing a small molecule to double oxygen delivery isn't quite as simple as it sounds. It took decades of work for Claude Nicolau, founder and chief science officer of NormOxys, just to develop a compound that binds hemoglobin allosterically in such a way that it releases two oxygen molecules. And then the scientist still had to find a way to get the binding agent inside red blood cells.

That's an issue that required "some really innovative chemistry to resolve," especially so the molecule wouldn't diffuse back out of the red blood cells after entry, said Karabelas. To achieve this scientific feat, the company recruited Nobel laureate Jean-Marie Lehn, who is a chemistry chair at the Collège de France in Paris as well as the University of Strasbourg's Director of the Laboratory of Supramolecular Chemistry.

Lehn, no stranger to the start-up world, having founded Alantos and AC Immune, succeeded in co-opting a specific transporter on the surface of erythrocytes to get the molecule inside the cell. He then created a single compound, OXY111A, which combined this transporter-binding ability with the capacity to attach allosterically to hemoglobin.

Because OXY111A can be used to treat a variety of diseases caused by low oxygen levels - from chronic kidney disease to traumatic blood loss to CHF and cancer - the start-up also faced the additional challenge of identifying the initial therapeutic arenas best suited for testing the molecule. According to Karabelas, NormOxys and its board solicited opinions from multiple key opinion leaders before ultimately deciding based on unmet medical need and scientific rationale on CHF and oncology as the first diseases in which to test OXY111A.

"Clearly, the animal models are positive and indicate [OXY111A] could be very successful in humans" with CHF, said Karabelas. But cancer also offered an "intriguing" possibility, he said, in part because of a growing body of evidence suggesting severely hypoxic conditions actually drive tumor growth.

The link between hypoxia and cancer metabolism is somewhat counter-intuitive given the current emphasis by oncologists on anti-angiogenesis, which attempts to starve a tumor cell of oxygen and nutrients by shutting blood vessel formation in these cells. But cancers are notorious for finding ways to circumvent normal cellular processes that might lead to their destruction. Indeed, it's now recognized that when starved for oxygen, tumor cells increase production of a specific protein called hypoxia-inducible factor-1 alpha (HIF-1a) that activates both the angiogenesis pathway as well as certain transporters responsible for pumping out chemotherapeutic agents, resulting in treatment-resistant cells.

As in CHF animal models, early data in animal models of melanoma, hepatoma, pancreatic and colon cancers have produced dramatic results, according to Tolar. Weekly intravenous injection of OXY111A in rats with liver cancer completely inhibited tumor growth and led to the disappearance of tumors, while treatment with doxorubicin alone simply retarded cancer growth.

In an announcement issued separately from the financing news, NormOxys also revealed the initiation of a Phase I clinical trial in healthy volunteers that is the first step to moving OXY111A into patients with CHF and an as yet undisclosed cancer indication. The Phase I study, which is designed as a randomized, ascending dose trial, will assess the safety, tolerability and pharmacokinetics of a single intravenous dose of the drug in healthy volunteers.

### **Proof-of-concept data and then a partnership**

In both indications, Tolar says the Series B money will allow NormOxys to obtain proof-of-concept data with a relatively limited number of patients, on the order of 50 in each indication. "We aren't talking about

large-scale studies with hundreds and hundreds of patients,” he said. At that point, the biotech will actively seek a partner - or partners.

Both Tolar and Karabelas declined to specify the biotech’s deal-making strategy. Apparently a number of pharmaceutical companies have already signed confidentiality agreements but the biotech intends to keep them at arms’ length until it has more clinical data. “The right answer is ‘we’ll see.’ It depends on what kind of data we get,” said Karabelas. “Having said that, our desire would be to have one partner recognize the full value of the platform and the molecule.”

Karabelas’ statement suggests the company might prefer a big sibling, similar to what Agios found in Celgene when it recently partnered its cancer metabolism platform, or Regeneron established with Sanofi-Aventis. In terms of a sale, the goal presumably would be an exit similar to the one Sirtris achieved in 2008, when GlaxoSmithKline acquired the sirtuin drug developer for \$720 million.

NormOxys’ ability to ink that kind of lucrative partnership is far from certain - even if it demonstrates compelling clinical data. Tolar has suggested the company will take a platform approach developing a group of related molecules for different indications. But since second-generation oxyrens have yet to reach the IND-enabling phase, for now the majority of the biotech’s value is contained in one candidate, OXY111A.

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