

PHARMACEUTICALS

# CoLucid Pharmaceuticals

First-in-class CNS drugs

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**Contact:** James F. White, PhD, CEO  
**Business:** In-licensing and developing CNS drugs

**Founded:** December 2005

**Founders:** Pappas Ventures

**Employees:** 10

**Financing to Date:** \$41.5 million

**Investors:** Pappas Ventures; Domain Associates; Care Capital; Pearl Street Ventures; Triathlon Medical Ventures

**Board of Directors:** Art Pappas (Pappas Ventures); Jesse Treu, PhD (Domain Associates); Richard Markham (Care Capital); James White

**Scientific Advisory Board:** Nabih Ramadan, MD (Rosalind Franklin University of Medicine and Science); Peter Goadsby, MD, PhD (National Hospital for Neurology and Neurosurgery, Queen Square, and the Hospital for Sick Children, London); J. David Leander, PhD, MBA (Neuropharm Consulting)

For 22 years, James White worked for Indianapolis-based **Eli Lilly & Co.**, eventually rising to head its neuroscience research. In 2001, he became head of R&D for Lexington, Massachusetts-based Hypnion Inc., a company that focuses on sleep disorders. He went on to co-found Dynogen Pharmaceuticals Inc., a Massachusetts company that targets gastrointestinal and genitourinary disorders, but his heart never really left Indiana.

He frequently reminisced with Arthur Pappas, head of the investing firm Pappas Ventures and a member of Dynogen's board, who shared his interest in starting companies in areas. The two talked often of starting a company in Indiana if they ever got the chance.

That opportunity came in 2005 when they heard that Lilly was paring down some of its assets and preparing to out-license some of them. One of those programs was a promising migraine drug. Pappas negotiated for the rights and started **CoLucid Pharmaceuticals Inc.** in December of that year.

The drug was one of a new class of molecules known as neurally acting anti-migraine agents (NAAMA). It is in some ways a successor to the triptans, which were introduced in the 1990s and provided relief to a great many patients. Triptans were developed for their vasoconstrictor activity, based on the working theory of the time that migraines were caused by swollen blood vessels along the surface of the brain. The swelling produces signals that are transmitted by trigeminal nerves, which also release substances that cause dilation of blood vessels and lead to activation of sensory neurons. But the receptors targeted by triptans also controlled constriction of coronary arteries, which led to safety issues that continue to haunt the triptans today.

Further research revealed that the vasoconstriction is caused by the drug's influence on 5-HT<sub>1B</sub> receptors. But triptans confer migraine relief primarily through the related 5-HT<sub>1D</sub> receptors. Lilly's drug selectively targeted the 5HT<sub>1F</sub> receptor, which plays a central role in the trigeminal nerve pathway. As a result, the drug appeared to eliminate the cardiovascular side effects linked to the triptans.

That drug, now known as COL-144, completed a Phase II trial with an intravenous formulation in 2007 and showed no evidence of cardiovascular side effects. The drug demonstrated at least equal efficacy to triptans in the control of migraine symptoms. A Phase II trial to explore higher doses with an oral formulation is planned for early next year with Phase III studies slated to start by the end of 2009.

The migraine market is significant. Migraines are often chronic, and some estimates put the incidence at 10 to 15% of the population. **GlaxoSmithKline PLC's** drug sumatriptan (*Imitrex*), a triptan, was launched in 1993 and remains the market leader with about \$1.4 billion in annual sales. "The health economics story is huge, because when you go down for the count with a migraine you're out for that day and maybe the next day, too," says White. The condition costs US employers about \$13 billion annually in lost productivity, he says.

A competing tack for migraine medications are the CGRP (calcitonin gene-related peptide) antagonists. **Merck & Co. Inc.** leads the field, White says, having reported some promising Phase III trial results at the American Headache Society meeting in June. CGRP acts in the trigeminal nerve pathway, which transmits migraine to higher brain centers. COL-144 acts earlier in the pathway--by activating 5HT<sub>1F</sub> receptors, it

prevents the release of CGRP. "The two molecules are two variations on the same theme. It isn't really clear" which approach will have an advantage, White says.

There is other competition from firms developing pain medications. Companies often test their drugs against migraines because migraine clinical trials are in some ways easier and cheaper to run than other chronic pain trials. Migraines tend to be short-lived, which provides a clear clinical end point to be measured. "You can get a Phase II trial enrolled and the results understood in six months. Some of these other chronic pain conditions are trickier to measure responses," says White. With chronic conditions, patients might have to be on a drug for days or weeks to have an effect. With migraine, "you know within two hours if your drug worked or not," says White.

As a result, many new drugs are tested against migraine. "People are throwing everything against the wall to see what will stick. There's a pretty good market there if something happens to hit, and they're learning [about their compound] by doing those studies," White says.

CoLucid is also delving into the sleep disorder market, using a technology licensed from **Sention Inc.** The approach is to create a conjugate of a cholinesterase inhibitor and a second drug. The cholinesterase inhibitors can pass the blood-brain barrier and are already used to improve cognitive function in Alzheimer's patients. Once there, the secondary drug is gradually released and can provide an additional therapeutic benefit. Anti-depressants are a logical choice for the secondary drug because depression is a common co-morbidity to Alzheimer's disease. "It's actually delivering two distinct therapies to the brain," says White. The approach allows the delivery of the second drug to distinct parts of the brain--a different profile than would be achieved if the drug were administered on its own.

CoLucid is initially going after wake-promoting indications. Existing drugs can be addictive and have a side effect of hypersomnolence--an overwhelming urge to sleep after the wakefulness effect wears off. "That's why truck drivers who take some of these

concoctions fall asleep at the wheel," says White. So far, some of the combinations CoLucid has tested in animals are as powerful as amphetamines, but show no signs of addiction or hypersomnolence, White says.

**Cephalon Inc.**'s drug modafinil (*Provigil*) is the leader in the wake promotion market. Initially approved for narcolepsy, it has found use by night shift workers and for jet lag. Somnolence is a common problem for a number of central nervous system diseases such as depression. Alzheimer's patients often experience "sundowning"--a period in late afternoon where they have little interest in interacting.

CoLucid plans to study the effect of the drug in sleep studies, and then position it initially in populations that want to stay awake longer than normal, such as military personnel and fire and rescue teams. "If there was a drug that could help people set aside the need for sleep for 24 hours and still have excellent cognitive function, that would be a drug people would be interested in," says White.

The drug will likely enter Phase I trials in the first quarter of 2009. "We feel good that it will make it through early clinical trials because it's a conjugation of two approved drugs. We're not likely to pick up any new activity because we know through binding

studies that it doesn't hit any receptors that the drugs don't hit on their own, says White.

With the wake-promotion drug, White expects FDA to be very strict about demonstrating the lack of addiction. *Provigil* is a schedule IV drug, meaning it is viewed as having a risk of dependence and abuse. "If we want to position away from being seen as a classic CNS stimulant, we'll have to have adequate data to demonstrate that the drug should not be scheduled. If we're trying to differentiate from the market leader, we'll be asked tough questions," says White.

CoLucid has raised \$41.5 million since its founding, most recently a \$25 million Series B round in July 2008 from new lead investor Care Capital and returning investors Pappas Ventures, Domain Associates, Pearl Street Venture Funds, and Triathlon Medical Ventures. While the company will consider partnering, it also wants to keep its options open. "It would be smart to have some potential partners lined up for Phase III trials, but if COL-144 continues to look as promising as it does now, it might inspire our investors to fund Phase III trials on their own," says White.

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—JIM KLING