

# VeroScience: Applying Nature's Genius to Help Improve the Human Condition

DONNA COWAN, CCRC; ANTHONY CINCOTTA, PhD

## ABSTRACT

VeroScience is a biotechnology company in Tiverton, Rhode Island, focused on the development of therapies and products to improve human health. The company has a strong pipeline of metabolic disease products and therapies for immunological disorders. A major platform technology of the company, Circadian Neuroendocrine Resetting Therapy, is utilized as a generator of multiple therapeutic strategies to treat a variety of disease states. The circadian timed daily (morning) administration of Cycloset<sup>®</sup>, a quick release formulation of bromocriptine mesylate, a dopamine agonist, was developed for the treatment of type 2 diabetes using this platform technology.

**KEYWORDS:** Neuroendocrine Resetting Therapy, type 2 diabetes, cycloset, glycemic control

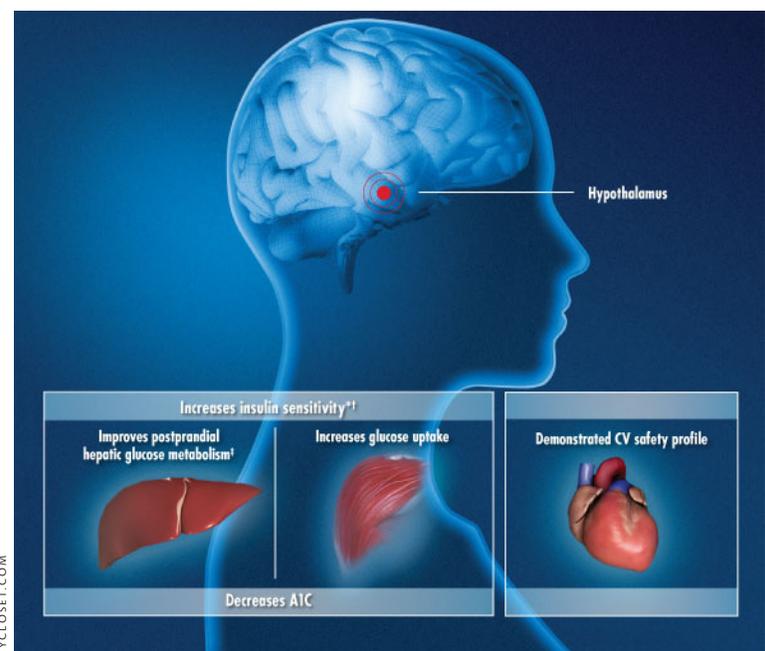
## INTRODUCTION

Since 2001, VeroScience has been in the business of developing drugs to treat metabolic and immune system disorders such as type 2 diabetes, obesity, and cancer through its platform technology, Neuroendocrine Resetting Therapy (NRT). The platform technologies of the company were co-developed by its founder, Anthony Cincotta, PhD, largely in academia during the 1980s, incorporated into a biotechnology company that he founded in 1990 and directed until 2000, ErgoScience, and then ultimately transferred to VeroScience in 2006. NRT is based on research demonstrating that normal physiology is regulated in large part by the temporal interactions of circadian neuroendocrine oscillations within certain centers of the brain. Alterations in the phase relations of these circadian activities alter physiological status of the organism. Resetting aberrations in these activities is an effective means of treating several neuroendocrine disorders.

In 1997, data presented at the 57th Annual Scientific Sessions of the American Diabetes Association (ADA) reported the results of three nationwide, multi-center trials, known as "TRIAD – Time Regulated Intervention in Adult Diabetes" conducted by ErgoScience demonstrating that Ergoset, a timed quick-release formulation of a dopamine agonist (bromocriptine mesylate), used alone or in combination with oral antidiabetic agents, was shown to produce statistically and clinically meaningful reductions in blood sugar

levels in obese, type 2 people with diabetes when compared to placebo. In 1998, ErgoScience filed for Food and Drug Administration (FDA) approval of the drug. The FDA initially issued a non-approval letter, owing to concerns about safety of the active agent, bromocriptine. ErgoScience appealed that decision and the FDA issued an approvable letter to ErgoScience for Ergoset in 1999. Thus began efforts for the successful transition of NRT, including Ergoset, to VeroScience and eventual approval of the drug marketed as Cycloset.

After securing private funding in 2003 and 2006, VeroScience was able to initiate the required FDA 3,000-person, one-year trial to evaluate the overall safety and cardiovascular safety of Cycloset. The trial was conducted at 74 sites in the United States, including 22 Veterans Affairs Medical Centers. Briefly, patients with type 2 diabetes were randomized 2:1 to bromocriptine-QR (Cycloset) or placebo in conjunction with the patient's usual diabetes therapy (diet controlled only or up to 2 anti-diabetes medications, including insulin). The all-cause safety endpoint was the occurrence of any serious adverse event (SAE). In a pre-specified analysis, the frequency of cardiovascular (CVD) events defined as a composite of myocardial infarction, stroke, coronary revascularization, hospitalization for angina or congestive heart failure was evaluated.



## RESULTS

Results showed that 176 (8.6%) people in the bromocriptine-QR group reported SAEs compared to 98 (9.6%) in the placebo group, and a lower percentage of people reported a CVD endpoint in the bromocriptine-QR group; 37 (1.8%) versus placebo, 32 (3.2%). In fact, these results demonstrated a 40% relative risk reduction in the CVD endpoint among those taking bromocriptine-QR. Nausea was the most commonly reported adverse event in the bromocriptine-QR group. Mean HbA1c was lower in the bromocriptine-QR group than in the placebo group at one year.<sup>3</sup>

Based on these safety and efficacy results, the FDA granted marketing approval to VeroScience for Cycloset in May of 2009. Cycloset is approved by the FDA, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It has been shown to reduce post-prandial hyperglycemia without increasing insulin levels and while not increasing the risk for hypoglycemia or weight gain.<sup>2</sup> Cycloset was the first diabetes therapy to be approved under the FDA's new cardiovascular guidelines (December 2008) requiring evidence that type 2 diabetes medications do not increase the risk of cardiovascular disease.<sup>4</sup> In additional analyses, five times as many Cycloset-treated patients achieved an A1C goal of  $\leq 7.0\%$  compared to placebo.<sup>5</sup> Cycloset is marketed in the United States by Santarus Pharmaceuticals, Inc., in San Diego, California.



VeroScience is headquartered in Tiverton.

## ABOUT THE COMPANY

VeroScience is a hybrid of traditional academic inquiry and industrial focus within a small and efficient organization of six full-time employees in the 27,000 sq. ft. building. The facility houses an animal lab, bench laboratory, greenhouse and offices. There are scientists, an animal care professional and a medical/clinical affairs group within the company and several worldwide consultants. The company conducts preclinical and clinical research nationwide, utilizing strong academic and pharmaceutical industry collaborations to advance its development programs.

## BACKGROUND – PRECLINICAL STUDIES AND DEVELOPMENT RATIONALE

Decades of work investigating animals in the wild that undergo marked annual cycles of metabolism revealed that seasonal shifts from the obese, insulin-resistant condition to the lean, insulin-sensitive state are driven by shifts in the circadian phase relations of specific hypothalamic neurophysiological events.

By mimicking this neurophysiological shift by pharmacological interventions, it is possible to effectuate the predicted shift in seasonal metabolism in either direction, to or from the insulin-sensitive state. Similar approaches in a variety of genetic and diet-induced animal models of type 2 diabetes have produced similar results.<sup>1</sup>

Animals in the wild under natural conditions express a marked annual cycle of metabolism, shifting between lean insulin-sensitive, and obese insulin-resistant states at specific times of year. Seasonal insulin resistance imparts the ability to withstand long periods of ensuing low food availability and this seasonal mechanism appears to have evolved as a survival strategy to circumvent such an environmental stress. Among the many examples of such seasonal variations in metabolism are bear hibernation, bird migration, and squirrel overwintering. Available evidence indicates that this seasonal mechanism evolved and has persisted over at least 400 million years. Neuroendocrine and neurophysiological studies of seasonal animals among all the major vertebrate classes have implicated an important role for circadian dopaminergic input to the hypothalamus and specifically to the mammalian biological pacemaker (the suprachiasmatic nuclei, SCN) in the regulation of whole-body fuel metabolism.<sup>1</sup>

## METABOLIC DISEASE

By employing methods that mimic the neurobiochemical physiology responsible for the seasonal shift from the obese, insulin-resistant condition to the lean, insulin-sensitive state common among vertebrate species in the wild, it is possible to develop new treatment strategies for human metabolic diseases such as type 2 diabetes, obesity, and metabolic syndrome. Changes in the circadian phase relations of distinct neuroendocrine rhythms drive the annual cycle of metabolism among vertebrates in the wild.

Consequently, it is not merely supplying the neuroendocrine factors of the “lean” season that produces leanness but rather supplying the circadian neuroendocrine blueprint that accomplishes this shift. Methods aimed at doing so can function to alleviate and induce the obese, insulin-resistant condition as is the case in the wild. VeroScience is developing different ways of applying this science to provide effective and practical means of treating human metabolic diseases.

**METABOLIC AND IMMUNE DISEASE RESEARCH AND THERAPY DEVELOPMENT**

VeroScience is committed to developing novel, practical, and effective therapies for chronic debilitating human diseases such as type 2 diabetes, metabolic syndrome, autoimmune disease, and cancer through interdisciplinary basic research.

Our approach to achieving these goals focuses in large part upon readjusting aberrant central nervous system (CNS) modulation of neuroendocrine activities etiologic in or supportive of these disease states.

VeroScience researchers study biological clocks in vertebrates and their organizational influence on neuroendocrine regulation of physiology to develop new treatment strategies for metabolic and immune disorders.

By investigating and mimicking nature’s means of regulating biochemical physiology for survival of vertebrates in the wild, VeroScience develops treatment strategies, not products per se, aimed at re-directing pathological biochemistry back towards its ‘normal’ physiological organization.

**IMMUNE DISORDERS**

Immuno-suppression and autoimmune diseases are both associated with derangements in the circadian neuroendocrine axis. Once again, it is the critical role of the brain-neuroendocrine axis to regulate and orchestrate the complex immunological interactions that occur at the cellular and tissue levels for the production of an organismal level immunocompetence.

Rather than focusing on specific immunomodulators such chemokines or lymphokines to boost immuno-reactivity, VeroScience focuses on resetting circadian neuroendocrine events that organize overall global immunophysiology to treat immuno-suppressed states. Similarly, autoimmune disorders with genetic components manifest as alterations in the neuroendocrine axis which in turn potentiate the underlying disorder.

Consequently, autoimmune diseases may be improved by appropriately resetting specific aberrations in the circadian neuroendocrine axis. Our interventions are not just pharmaceutical compounds but rather therapeutic treatment regimens employing such compounds in a particular manner to reprogram the master control centers in the brain for the production of whole-body immunological status.

**References**

1. Cincotta A. Hypothalamic Role in the Insulin Resistance Syndrome. In: Hansen B, Shaffrir E, eds. *Resistance and Insulin Resistance Syndrome*. London: Taylor and Francis; 2002:271-312.
2. Cycloset Package Insert. 2010; FDA approved label. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020866s002lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020866s002lbl.pdf)
3. Gaziano JM, Cincotta AH, O’Connor CM, Ezrokhi M, Ruty D, Ma ZJ, Scranton RE. Randomized clinical trial of quick-release

bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care*. 2010 Jul;33(7):1503-8.

4. Gaziano JM, Cincotta AH, Vinik A, Blonde L, Bohannon N, Scranton RE. Effect of Bromocriptine-QR (a Quick-Release Formulation of Bromocriptine Mesylate) on Major Adverse Cardiovascular Events in Type 2 Diabetes Subjects. *J Am Heart Assoc*. 2012 Oct; 1.
5. Vinik A, Cincotta AH, Scranton RE, Bohannon N, Ezrokhi M, Gaziano JM. Effects of Bromocriptine-QR on Glycemic Control in Subjects with Uncontrolled Hyperglycemia on One or Two Oral Anti-Diabetes Agents. *Endocrine Practice*. 2012; 18(6): 931-943].

**Authors**

Donna Cowan, a Certified Clinical Research Coordinator, is project manager for VeroScience’s Medical Affairs and Clinical Research Operations.

Anthony Cincotta, PhD, is the founder of VeroScience.

**Correspondence**

Donna Cowan  
 VeroScience, LLC  
 1334 Main Road  
 Tiverton RI 02878  
 401-816-0525  
 Fax 401-816-0524  
[donna\\_cowan@veroscience.com](mailto:donna_cowan@veroscience.com)

**Important Safety Information**

**Contraindications**

CYCLOSET is contraindicated in:

- Patients with known hypersensitivity to bromocriptine, ergot-related drugs, or any of the excipients in CYCLOSET.
- Patients with syncopal migraine. Bromocriptine increases the likelihood of a hypotensive episode among patients with syncopal migraine. Loss of consciousness during a migraine may reflect dopamine receptor hypersensitivity. CYCLOSET is a dopamine receptor agonist, and may, therefore, potentiate the risk for syncope in these patients.
- Women who are nursing their children. CYCLOSET may inhibit lactation. There are postmarketing reports of stroke in this patient population although causality has not been proven.

**Warnings and Precautions**

- Hypotension: Can cause orthostatic hypotension and syncope, particularly upon initiation or dose escalation. Use caution in patients taking anti-hypertensive medications. Assess orthostatic vital signs prior to initiation of CYCLOSET and periodically thereafter. Advise patients during early treatment to avoid situations that could lead to injury if syncope was to occur.
- Psychosis: May exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis. Use in patients with severe psychotic disorders is not recommended.
- Somnolence: May cause somnolence. Advise patients not to operate heavy machinery if symptoms of somnolence occur.
- Interaction with dopamine antagonists: Concomitant use with dopamine antagonists such as neuroleptic agents may diminish the effectiveness of both drugs. Concomitant use is not recommended.
- Other dopamine receptor agonists: Effectiveness and safety are unknown in patients already taking dopamine receptor agonists for other indications. Concomitant use is not recommended.
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with CYCLOSET or any other antidiabetic drug. CYCLOSET does not increase the risk of macrovascular events.