BIOTECHNOLOGY

Atterocor Inc.

Treating adrenal cancer with an ACAT1 inhibitor

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Contact: Julia C. Owens, PhD, President & CEO
Business: Treatment for adrenal cancer
Founded: January 2012
Founders: Raili Kerppola, PhD; Gary Hammer, MD, PhD; Julia C. Owens
Employees: 6
Financing To Date: $16 million
Investors: Frazier Healthcare; 5AM Ventures; Osage University Partners; Regents of the University of Michigan; Michigan Pre-Seed Capital Fund
Board Of Directors: Carol Gallagher, PharmD (formerly Calistoga Pharmaceuticals); Bill Harrington, MD (Osage University Partners); Julia C. Owens; Jamie Topper, MD, PhD (Frazier Healthcare); Randall Whitcomb, MD (Frazier Healthcare)
Scientific Advisory Board: Gary Hammer, Chairman (University of Michigan); Wiebke Arlt, MD, DSci (University of Birmingham); Euan MacIntyre, PhD (Galleon Pharmaceuticals); Lawrence L. Rudel, PhD (Wake Forest University); Laura Shawver, PhD (Cleave Biosciences); Roger Ulrich, PhD (founder, Calistoga Pharmaceuticals)

The name ***Atterocor Inc.*** says plenty about this Michigan-based start-up: "attero" is Latin for "destroy" and "cor" stands for cortical cells. The company aims to destroy, or at least interfere with, pathological processes in cortical cells of the adrenal glands. Adrenal glands come in pairs; they sit atop the kidneys. The cortex is the outer layer of the adrenal gland and is responsible for secreting hormones including cortisol, primarily in response to stress.

Atterocor has begun a Phase I trial on a compound it calls ATR-101 in people with adrenocortical carcinoma, or adrenal cancer, a truly rare and fatal disease. In the US, there are only 500 or so new diagnoses yearly, and only about 1,000 persons living with adrenal cancer. CEO Julia Owens thinks her firm has something that might help these individuals, whose current treatment options are poor. She describes ATR-101 as "a novel ACAT1 inhibitor that induces apoptosis [programmed cell death] in adrenocortical cells." ACAT1, also known as Acyl-CoA cholesterol acyltransferase, is an enzyme that catalyzes the intracellular esterification of cholesterol and promotes its storage in a variety of tissues including the adrenal gland, where it serves as a key reserve for steroid biosynthesis.

ACAT was widely studied throughout the 1980s and into the mid-90s. Several companies tested ACAT inhibitors in hopes of shutting down cholesterol biosynthesis and thereby lowering serum cholesterol levels, Owens notes. But after some of the compounds were shown to lack efficacy, and others proved toxic, ACAT inhibitors fell from favor and statins emerged as the preferred way of lowering cholesterol.

Owens emphasizes that Atterocor's compound specifically inhibits ACAT1, and says the compound has "specific and novel effects on the adrenals, and can inhibit steroid synthesis in these glands." The company is saying little more than that about ATR-101, but it expects to reveal more over the coming year or so, as clinical trial data give the start-up more insight into the inhibitor's effects in the human body. "One of our goals is not just to modulate cancer, but also to reduce steroid levels, because excessive levels of hormones lead to a plethora of metabolic consequences such as high blood pressure and obesity, that can be independently life-threatening," Owens explains.

Atterocor has no intention of developing ATR-101 as a treatment for other solid tumors and the large markets they represent, she asserts. It is common practice for companies, particularly small ones, to seek regulatory approval for an "orphan" indication and then try to expand the drug's label – or entice a bigger partner to do so. Atterocor is, however, considering other adrenal diseases where ATR-101 could benefit patients, Owens acknowledges, although she declines to specify one.

Cushing's syndrome could be an ideal secondary indication for ATR-101, given that the disorder is associated with prolonged exposure to high levels of cortisol. The disease is a rare one that has not been studied much; incidence reports are rising as clinicians get better at diagnosing it. Symptoms include upper-body obesity, extra fat above the collarbone and on the back of the neck, a moon face, and thinning arms and legs. People who take high doses of corticosteroid drugs like prednisone to treat diseases such as arthritis sometimes develop the syndrome. Such cases are considered "exogenous" and are generally treated by removing whatever caused the problem.

The first oral drug for endogenous Cushing's syndrome, which arises from within the body, won FDA's approval in February 2012. **Corcept Therapeutics Inc.**'s *Korlym* is a new formulation of mifepristone, widely known since the 1980s as RU486 and used as an abortifacient. In its new incarnation, the drug is a cortisol receptor blocker indicated to control hyperglycemia in certain subsets of Cushing's patients. The first drug to treat Cushing's disease, a subset of Cushing's syndrome caused by high ACTH levels from a pituitary tumor, was approved by FDA in December 2012. **Novartis AG**'s *Signifor* (pasireotide) won approval based on its ability to lower cortisol levels.

For now, it's clear that Atterocor's focus is on treating adrenal cancer, and it is by no means the only organization pursuing this teeny market. Rare disease research is in vogue these days, as companies of all sizes have recognized that regulators are eager to approve treatments for underserved patients, payors are willing to reimburse at what can be hefty rates, and foundations and patient advocacy groups can help firms in many ways including financial. So it's hardly surprising that the **National Cancer Institutes**' database currently lists 15 active clinical trials of treatment approaches for adrenocortical carcinoma. Pasireotide is one of the new molecules in testing, and several approved cancer drugs are also being tested separately and in combinations.

Given the rarity of adrenal cancer, "It

can be challenging to find enough patients to conduct a study," Owens points out, but she believes Atterocor will be able to do so at just two clinical trial sites: the **University of Michigan** (UM) Comprehensive Cancer Center and the **University of Texas' MD Anderson Cancer Center**. UM sees about 200 adrenal cancer patients a year, she notes, making it "probably the world's leading adrenal cancer treatment center." The company has strong affiliations there, as one of its three co-founders is Gary Hammer, director of the Endocrine Oncology Program at the university.

> "If we get a clear signal the molecule is working, we can move along a clear path to approval for a relatively small amount of money." - Randy Whitcomb, MD

Hammer has since 2005 also borne the title of "Millie Schembechler Professor of Adrenal Cancer." Millie was the wife of Michigan's famed football coach Bo Schembechler, and after she died of adrenal cancer he endowed a professorship and funded a research program at the university in her name. Through the years, Hammer has become highly regarded for his expertise with this form of cancer, both as a researcher and a clinician. But the idea to try treating adrenal cancer with an ACAT inhibitor was conceived by a patient of Hammer's named Raili Kerppola. A scientist working independently while on medical leave, she collaborated with Hammer and her husband, UM biological chemistry professor Tom Kerppola, to synthesize and test compounds.

People are often diagnosed with adrenal cancer when it has already metastasized, Owens explains. Sometimes individuals report having suddenly put on weight and developed high blood pressure. Others come in with pain in the gut that turns out to be from a large tumor. Or they get a CT scan for a completely different reason, and an adrenal tumor is seen. Altered levels of adrenal steroids including cortisol are one way of confirming the diagnosis of adrenal cancer, and Owens notes that the same standard assays will help Atterocor assess whether or not ATR-101 is helping people.

Like most patients diagnosed with this form of cancer, Kerppola was first treated with *Lysodren* (mitotane), a derivative of DDT that can slow or halt growth of adrenal cancer by altering steroid metabolism. Approved in 1959, it has become a standard therapy for tumors that cannot be removed through surgery. The side effects of this highly toxic drug are terrible, Owens notes. "It takes three to four months to get blood levels of mitotane up to the point where the drug may do some good, but long before then most patients experience massive gastrointestinal troubles and CNS issues. Since the average life expectancy after diagnosis for many patients is only one year, a lot of patients don't want to tolerate the side effects." Recently, she notes, the European Network for Study of Adrenal Tumors and other researchers worldwide tested mitotane in combination with different combinations of chemotherapies, hoping to show that one regimen worked better than another. But in the study involving approximately 300 patients, the best overall response rate was only 23%. "That shows you how low the bar is," Owens asserts.

Raili Kerppola got no benefit from mitotane, and so elected to undergo chemotherapy. When that too failed to help stop the cancer, Owens recalls, Kerppola said to Hammer, "I am going to find you a compound that *works*." She survived 2.5 years after being diagnosed with the disease, long enough to identify the compound now known as ATR-101 and to assign her inventorship rights to Atterocor. The start-up also licensed rights to the compound from UM. Kerppola succumbed to the disease in June of 2013. "Her battle against adrenal cancer has motivated us tremendously," Owens declares.

In October, Atterocor announced that it had embarked on a Phase I trial for ATR-101 in 21 adrenal cancer patients. Owens describes it as a "3 + 3" clinical trial design, wherein three patients are given a beginning dose and if they do well, three more people are given a higher dose, and so on." In addition, Atterocor announced that it has secured FDA and the European Medicines Agency orphan drug designation for the compound.

Venture capitalists had originally been tempted when Owens told them that Atterocor could enter the clinic in a year and have vital data just a year after that. But Frazier Healthcare general partner Jamie Topper says his initial response to the pitch was that adrenal cancer was an "ultra-orphan indication," too small to pursue. As he and Randy Whitcomb, a Frazier advisor who just happens to be an endocrinologist, proceeded with their due diligence, the appeal grew. Topper asserts, "It became obvious that this is a tremendous unmet need. If you are unfortunate enough to be diagnosed with adrenal cancer, you are extremely likely to die in a relatively short time." He figures that a company able to develop an effective treatment will see it used in each patient, even if the first therapy is surgery to remove a tumor.

"Because of the limited patient population, Atterocor can be very targeted in its development," Whitcomb points out. "This is not a 1,500-subject, all-comer trial. If we get a clear signal the molecule is working, we can move along a clear path to approval for a relatively small amount of money." If the drug passes muster with regulators, then a well-defined and modest sales effort will suffice, he notes. "We can go to four or five thought leaders. We don't need a 100-person sales force."

In an August 2012 Series A round of financing, Atterocor raised $16 million from investors including Frazier Healthcare; 5AM Ventures; Osage University Partners; The Regents of the University of Michigan, and The Michigan Pre-Seed Capital Fund. [A#2013900211]

— Deborah Erickson

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