

# START-UP



## Windhover's Review of Emerging Medical Ventures

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### Ascenta Therapeutics Inc.

*Treating cancer by triggering apoptosis*

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**Industry Segment:** Biotechnology

**Business:** Oncology drug development

**Founded:** November 2003

**Founders:** Shaomeng Wang, PhD; Dajun Yang, MD, PhD; Marc Lippman, MD

**Employees:** 40

**Financing to Date:** \$35.5 million

**Investors:** Domain Associates; Sofinnova Ventures; Enterprise Venture Partners; Bank of America Venture Partners; US Venture

**Board of Directors:** Lou Bock (Bank of America Venture Partners); Marc Lippman (University of Michigan); Mike Powell, PhD (Sofinnova Ventures); Andrew Senyei, MD (Enterprise Venture Partners); Mel Sorensen, MD (Ascenta); Shaomeng Wang (University of Michigan); Eckard Weber, MD (Domain Associates)

There's no doubt that the paradigm for cancer treatment is shifting. Conventional chemotherapeutic agents are still effective and a vital part of the armamentarium, but doctors are increasingly trying to offset the toxicity of older drugs by combining—or replacing—them with biological agents that more precisely target cancers. Though biologicals are easier on patients' bodies than cytotoxic agents, at \$80,000 to \$100,000 or more for a year's course of therapy, their high cost is having a brutal impact on health-care costs.

So it's hardly surprising that payers

around the globe are scrutinizing the value that new high-priced medicines deliver to patients. Because not even the priciest drugs offer actual cures for cancer, and some extend life by just a few months, many industry observers believe the ultra-premium pricing that biological drugs currently command is unsustainable. Prudent start-ups now taking aim at the oncology market are paying as much heed to the overall economic and prescribing trends in the field as to the competition and their own technology platforms.

The managers of **Ascenta Therapeutics Inc.** believe they've got the

right technology and team to develop the sorts of drugs that will define the coming wave in cancer treatment. Orally bioavailable small molecules that hit key proteins mis-expressed in tumor cells—some of which are the targets of current biologics—have “the potential to make cancer a manageable disease,” declares Mark Benedyk, the start-up's VP, business development. He points to **GlaxoSmithKline PLC's** Phase III drug candidate, lapatinib ditosylate (*Tykerb*) as an example of the new paradigm. *Tykerb* binds the same receptor as trastuzumab (*Herceptin*), **Genentech Inc.'s** successful antibody treatment for breast cancer, but it can be manufactured at a much lower cost because it's a small molecule rather than a protein.

Ascenta's portfolio of drug candidates aims to stop cancers by promoting apoptosis, the process of cell death that is ordinarily triggered once a cell develops numerous DNA mutations. In cancerous cells, the signaling mechanisms that would ordinarily trigger the apoptosis process are abnormal, so cells that would ordinarily apoptose don't die. Benedyk explains that, “usually in cancer, this failure to apoptose is due to signaling proteins that are mutated or over-expressed.” Ascenta's approach is to interfere with the machinery that governs those signals. Developing small molecules capable of interfering with protein-protein interactions requires a different approach to drug discovery than identifying compounds

that bind to receptors.

The company's most advanced candidate, AT-101, interferes with all of the four proteins (Bcl-2, Bcl-X<sub>L</sub>, Bcl-W, and Mcl-1) in the Bcl-2 family that are known to interact with other proteins central to generating a signal for a cell to either survive or apoptose. The best-known member of this family is the protein Bcl-2; the same one targeted by oblimersen sodium (*Genasense*), the antisense oligonucleotide developed by **Genta Inc.** and its partner Aventis (now **Sanofi-Aventis**). *Genasense* was rejected by the FDA as a treatment for melanoma in 2003, but it is again before the agency for review as a leukemia treatment.

Benedyk believes Ascenta's compound has the potential to compete quite favorably with *Genasense*, for several reasons. "*Genasense* is an antisense therapy that is administered intravenously, while AT-101 is an orally administered small molecule. *Genasense* inhibits the activity of only Bcl-2 itself, while AT-101 hits all four members of the family." To figure out where AT-101 will work best therapeutically, the company has put its lead compound into multiple Phase II trials. It's being evaluated as a single agent in chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), and prostate cancer, and it is also being tested in combination with other commonly prescribed drugs. Presently, AT-101 is in trials with **Biogen Idec Inc.**'s antibody rituximab (*Rituxan*) in CLL and NHL, and it is being used in prostate cancer in combination with Taxotere. The company plans additional trials of AT-101 with other standard chemotherapeutic agents in additional indications.

"We've placed bets on several squares," Benedyk says, and that's only prudent. As a small company with limited resources, Ascenta wants to be sure its drug is producing a solid clinical effect before it begins paying for a Phase III trial. So far, Benedyk says the drug appears to have an effect in patients in all the indications the company has chosen. He puts this

down to "the centrality of apoptotic pathways in the etiology of cancer," and to the fact that AT-101 hits multiple targets within those pathways.

AT-101 is derived from a compound known as gossypol, a natural product found in cottonseed oil. The native substance was identified many years ago, through studies on men from a village in China who had all become sterile because of long-term consumption of unprocessed cottonseed oil. Benedyk explains, "Inhibition of Bcl-2 family proteins in testicular cells involved in making sperm resulted in premature apoptosis of nascent germ cells, rendering these men sterile. This phenomenon illustrated the oral bioavailability and targeted nature of the active ingredient in AT-101."

Benedyk believes follow-on compounds to AT-101 and other drug candidates in Ascenta's pipeline demonstrate the scientific talents of Shaomeng Wang, an associate professor in the department of internal medicine at the **University of Michigan** who is one of Ascenta's co-founders. "He has a unique approach to medicinal chemistry, integrating natural product chemistry and traditional synthetic organic approaches with rational drug design. He thinks about the druggability of compounds early on in the discovery process," Benedyk asserts.

"Shaomeng's lab is a driving force behind our discovery engine," Benedyk declares. The scientist has already provided the start-up with several classes of compounds, many of which have been sent for evaluation to the wholly owned Ascenta preclinical research subsidiary in Shanghai. Benedyk says this "preclinical screening facility," currently staffed with 17 people, is a key part of Ascenta's business model. The company intends to leverage it by building a network of academic discovery alliances, like the one it now has with University of Michigan, and shipping compounds accessed through these connections to Shanghai.

"Costs in China are low, and the scientists are very good," Benedyk

asserts. Although most firms, even large ones, face a nearly insurmountable barrier to entry there, Ascenta is deliberately recruiting scientists who've been educated in the US and returned home.

The Shanghai operation is overseen by Dajun Yang, a company co-founder who serves as VP of research and general manager of Ascenta Shanghai. San Diego-based VP of manufacturing Ming Guo, PhD, spent eight years working in that area for **Pfizer Inc.**

Other staff in the US is predominantly focused on clinical development, "where you get the most value from a portfolio asset," Benedyk notes, listing a roster of experienced people who've joined Ascenta's management team. Ascenta's president and CEO is Mel Sorensen, MD, who formerly headed oncology clinical development at GlaxoSmithKline PLC and Bayer AG. The company's chief medical officer, Jon Holmlund, MD, spent several years at Isis Pharmaceuticals Inc. and at the National Cancer Institute. "Not many three-year-old companies have such a clinically focused team with a pipeline as robust as ours," Benedyk boasts.

In addition to compounds that act on members of the Bcl-2 protein family, Ascenta is also pursuing candidates that may restore normal function to cells by blocking interaction between the proteins Mdm2 and p53, both of which are central to cell death and survival. Ascenta is also working to create small-molecule mimics of a protein known as *Smac*, which inhibits an inhibitor of apoptosis known as the X-linked inhibitor of apoptosis or XIAP.

Ascenta is interested in partnering with large firms, particularly those whose products are likely to be synergistic with its own. Benedyk emphasizes that the start-up will insist on maintaining some control over the development of its drug candidates and the marketing of eventual products.

To date, Ascenta has received \$35.5 million from venture firms including Domain Associates, Sofinnova Ventures, Enterprise Venture Partners, Bank of America Venture Partners, and US Venture Partners. —**Deborah Erickson**