Altor BioScience Corp.

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Summary:	Altor BioSciences aims to exploit the intrinsic selectivity of T-cell receptors (TCRs) by pairing soluble receptors with therapeutic payloads. These TCR/drug combos are smaller than antibodies and could theoretically bind to targets within cells, not just on the cell surface, a main selling point of the firm's so-called STAR technology. At first Altor plans to enhance the safety and efficacy of existing marketed drugs by pairing them with monoclonal antibody-like TCRs for improved targeting.

Further Analysis:

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T-Cell receptors go where antibodies can t

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Contact: Paul M. Herron, VP Business Development & CFO

Industry Segment: Biotechnology

Business: Immunotherapy

Founded: August 2002

Founder: Hing C. Wong, PhD, President & CEO

Employees: 22

Financing to Date: $20 million

Investors: Sanderling Ventures; Sunol Molecular Corp.; TVM Capital; Audax Ventures

Board of Directors: Fred Middleton (Sanderling Ventures); Adam Waldman (The Endeavor Group); Hing C. Wong

Scientific Advisory Board: Linda Sherman, PhD (Scripps Research Institute); Norman Klinman, PhD (Scripps Research Institute); Hamilton Smith, MD (Nobel Prize Laureate, Venter Institute)

Monoclonal antibodies have been one of the true success stories of the biotechnology industry. They can be readily designed to target almost any protein or protein fragment (antigen) and are extraordinarily selective. They can be easily linked to therapeutic agents through chemical modifications. Products such as trastuzumab (*Herceptin*) and bevacizumab (*Avastin*) provide ample evidence of their commercial potential.

But they suffer a drawback: antibodies cannot enter cells, so they are limited to antigens that appear on the cell surface. Many potential protein targets, including some involved in cancer and infectious diseases, are found only in the interior of cells. Intracellular antibodies (or intrabodies) get around that problem. These antibody fragments are expressed within the cell and can target intracellular proteins, but they can be unstable and have very limited utility.

Altor BioScience Corp. is banking on another solution. Its *STAR* technology relies on a fundamental mechanism of the immune system in which foreign antigens are cleaved into smaller fragments and presented on the cell s surface in conjunction with a set of proteins called the major histocompatibility complex (MHC). T cells recognize the complex via the surface T-cell receptor (TCR). When a T cell finds a threatening antigen on a cell s surface, it can prompt various immune defenses to combat it. This process can also go awry if TCRs mistakenly target antigens on normal cells, leading to autoimmune disease, allergies, and graft rejections.

Hing C. Wong, the founder of Altor and now its president and CEO, envisioned the T-cell receptor as a mechanism to reach antigens that are normally out of the reach of antibodies. He reasoned that a soluble form of the TCR could be designed to target an antigen fragment. It would have to be modified to carry some therapeutic payload because the T cell itself would be out of the picture. Wong hastens to point out that he was not the first to think of the idea, but he and his colleagues solved numerous technical problems, beginning while Wong was director of the Biology Skill Center at Baxter. In 1996, he founded the therapeutic antibody company **Sunol Molecular Corp.** and continued to pursue the research even as the company focused on antibody development.

In 2000, Sunol made the decision to sell off some of its assets. The *STAR* platform was promising but still at an early stage of development, and the decision was made that Sunol should retain more advanced product candidates. Altor was spun off from Sunol in 2002 with seed money from the parent company, TVM Capital, and Audax Ventures, and later raised capital from Sanderling Ventures. Wong stresses that neither Baxter nor Sunol has any equity or ownership in Altor s assets today.

To design a *STAR* reagent, Altor researchers must identify the specific peptide fragments that are produced from a protein of interest--for example, an HIV envelope protein. Then they must select fragments that are displayed in high enough density on the cell surface to be therapeutically useful. With a target fragment in hand, the team can tailor its soluble T-cell receptor to recognize it. If the fragment appears at a low density, the *STAR* reagent can be further tweaked to improve its affinity for the fragment. "In a sense, we turn it into a monoclonal antibody, and we can manipulate it to have any mechanism we want to kill off a cell," says Wong.

The company has pursued the *STAR* technology primarily as a vehicle to target existing therapeutic drugs in hopes of increasing their safety and efficacy. Its lead compound, ALT-801, is a fusion of the powerful cytokine interleukin-2 (IL-2) with a soluble TCR protein that recognizes a fragment of the common tumor antigen p53. IL-2 is an approved anti-cancer therapeutic but finds limited use because of serious toxicities. Now in Phase I clinical trials, ALT-801 has "behaved much better" than IL-2 alone, says Wong. He anticipates that the agent will begin Phase II trials in the second quarter of 2009. Other products in the preclinical stage include the anti-p53 *STAR* reagent fused to an antibody fragment and *STAR* reagents targeted to viral antigens from HIV, hepatitis C, and cytomegalovirus.

Altor has also licensed an antibody to treat staphylococcal infections in premature neonates to **Biosynexus Inc.** in Gaithersburg, MD. The compound is currently in a pivotal clinical trial. This antibody was originally in-licensed from the Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. Altor humanized the antibody to minimize the potential unwanted immunogenicity for human use and also created a high-production cell line for the antibody before licensing it to Biosynexus.

Altor also offers research reagents based on the *STAR* technology. Antigen presentation is a hot area of immunology research, and the reagents can be used to study antigen presentation in cancer and cells infected by viruses.

Wong points to two potential markets that are a natural fit with the *STAR* platform to reach intracellular antigens. Many proteins that play a role in cancer are intracellular, including p53, which can initiate DNA repair or apoptosis in damaged cells. Like most proteins, p53 is digested into peptides and presented at the cell surface. "It s a tremendous opportunity--we can target something that the monoclonal antibody people cannot do," says Wong.

Another potential market is infectious diseases that linger in the cell s interior, such as viruses, tuberculosis-causing bacteria, and malaria parasites. Antibodies can be used to prevent such agents from infecting a cell, but once in place they cannot be used to dislodge them. HIV is a particular concern because the virus is known to lie dormant in cells, forcing patients to take drug cocktails for the rest of their lives. "This kind of drug gives us the opportunity to really kill the virus off by eliminating the viral reservoir in infected patients," says Wong. Partly in recognition of that potential, Altor received a $100,000 research grant

from the Gates Foundation in October of this year.

Taken together, the oncology and infectious disease market opportunity could be worth about $13 billion, according to Paul M. Herron, who is Altor s CFO and VP of business development. But he and Wong both regard that estimate as conservative. The p53 protein is a recognized culprit in many cancers, including, non-small cell lung, breast, colorectal, and head and neck. "More than 50% of all cancers have overexpressed p53," says Wong.

Other technologies also target non-surface antigens. The UK company Avidex, acquired by **MediGene AG** in 2006, is also developing a soluble T-cell receptor, but the company s manufacturing process produces inactive proteins that must be activated in a separate step. It also relies on chemical conjugation to therapeutic or other functions, which can lead to problems with storage and pharmacokinetics. The design of the *STAR* molecule and its production in a well-characterized mammalian cell expression system, eliminates all of these shortcomings.

Altor is also well-positioned because of its strong intellectual property portfolio, says Wong. Monoclonal antibody technology is dominated by a wide variety of patents that must be navigated by any company developing a new reagent. But Altor s patent portfolio gives it full control over the entire process. "We don t really need to go to anyone," says Wong. **Jim Kling**