Juvaris BioTherapeutics Inc.

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Summary:	Juvaris BioTherapeutics Inc.'s technology is an offshoot of gene therapy work originally conducted at Valentis. Researchers there discovered that their DNA/lipid delivery combination elicited a mild immune response at the lowest dose. Juvaris has used the technology to develop two classes of products: JuvImmune is made up of the DNA/lipid combination without an antigen and is intended to boost the immune response. Combined with vaccines, where it boosts the intensity of the immune response, the technology is called JuvaVax.

Further Analysis:

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A New Perspective on Cancer Imunotherapy	*Start−Up*	Jun. 2007	2007900117
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START-UP
Windhover's Review of Emerging Medical Ventures

Juvaris BioTherapeutics Inc.

Immune system booster and vaccine adjuvant

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Industry Segment: Vaccines

Business: Immunostimulants for treating cancer, infectious and viral diseases

Founded: 2003

Founders: Martin D. Cleary; John F. Warner, PhD, CSO & VP, R&D Jeff Fairman, PhD, Senior Director of Research; Steven Dow, DVM, PhD (Colorado State University); Denny Liggitt, DVM, PhD (University of Washington)

Employees: 20

Financing to Date: $16.5 million

Investors: Kleiner Perkins Caufield & Byers

Board of Directors: Martin D. Cleary; Thomas P. Monath, MD (Kleiner Perkins Caufield & Byers); Mario Rosati (Wilson Sonsini Goodrich & Rosati); Lewis T. Williams, MD, PhD (Five Prime Therapeutics Inc.)

Scientific Advisory Board: Bali Pulendran, PhD (Emory University School of Medicine); David B. Lewis, MD (Stanford University School of Medicine); Denny Liggitt; Lawrence Corey, MD (Fred Hutchinson Cancer Center); Richard D. Klausner, MD (Klausner Consulting LLC); Stanley M. Lemon, MD (University of Texas); Steven Dow

Sometimes, research takes unusual turns. In the late ’90s and early 2000s, researchers at **Valentis Inc.** and **Genteric Inc.** were struggling to make gene therapy a reality. They packaged genes along with other DNA and greasy molecules known as lipids to help the DNA enter cells where it could be taken up and prompt the manufacture of the therapeutic protein.

The trouble was that protein production in target cells was weak and short−lived, no matter what they tried. "There was nothing you could do about it. We weren’t there, and we realized we weren’t going to get there," recalls Martin D. Cleary, who was president and CEO of Genteric at the time.

In search of other opportunities, Cleary learned of an intriguing observation made by his erstwhile competitors at Valentis. In a clinical trial, their DNA/lipid combination elicited a mild immune response at the lowest dose, prompting them to halt the study because they would have to increase the dose to achieve a therapeutic effect. The result made it a potential immunostimulant. Such a product has potential to enhance vaccines or as a therapeutic in its own right that could prompt the patient's immune system to fight off an infection, or even destroy tumors. Valentis didn't pursue that avenue because it remained focused on gene therapy.

Cleary saw the opportunity for a new company. Together with a group of others that had all been associated with Valentis, he founded **Juvaris BioTherapeutics Inc.** in 2003. The company licensed the relevant patents, excluding gene therapy rights, from Valentis in 2004 and purchased them outright in 2006. [W#200320364] "It's important to realize that this isn't gene therapy," says Cleary. The non−coding DNA is sufficient to cause an immune response. Juvaris is also pursuing patents covering the use of the technology for immune therapy. One has been issued.

Juvaris has developed two classes of products. *JuvImmune* is made up of the DNA/lipid combination without an antigen and is intended to boost the immune response. It can also be added to vaccines, where it boosts the intensity of the immune response by a factor of 50 to 100 over other vaccine boosting technologies. Put another way, it reduces the amount of vaccine required to achieve an equivalent response. Combined with vaccines, the technology is called *JuvaVax*.

JuvaVax has particularly interesting application to the influenza vaccine area, where supply shortages are a constant concern. The addition of *JuvImmune* to an influenza vaccine could theoretically stretch out even small batches of vaccine to help meet the seasonal demand.

An early sign of clinical success came from one of the founders, Steven Dow of **Colorado State University**, who had used the technology in a study of dogs with tumors that had failed chemotherapy. In several trials, he treated the animals with *JuvImmune* and *JuvaVax*. The results were impressive: in one study, 40% of dogs with hemangiosarcoma survived past 600 days when treated with chemotherapy in combination with *JuvaVax*. None of the dogs treated with chemotherapy alone survived past 200 days. In May 2004, Juvaris licensed Dow's technology for linking pattern−recognition receptor ligands to lipids. [W#200420398]

Those results made the company think about focusing on cancer, perhaps in combination with radiation or chemotherapy, to stimulate the immune system to eliminate metastases. But in 2005, they received surprising news from **Utah State University** researchers who were using *JuvImmune* to study a model for Rift Valley Fever virus, which is an important biodefense target. "One afternoon they called and said, 'we have something we've never seen before,'" recalls Cleary. The Utah State researchers had used *JuvaVax* to vaccinate mice against the virus, then exposed them to a lethal dose. One hundred percent of the animals survived. They also infected mice first and then treated them with *JuvaVax* afterward, and once again all of the mice lived. "In an instant, we became an infectious disease company focused primarily on viruses. That's one of the reasons that the first clinical study will focus on influenza," says Cleary.

That trial will be the first of two Phase I clinical studies planned for 2008. Beginning in March, one trial will compare the standard influenza vaccine with a *JuvaVax* preparation. "We expect to get an equivalent immune response with a much smaller dose of vaccine," says Cleary. Later in the year, the company plans to investigate using *JuvImmune* to treat chronic hepatitis B viral infections.

The immunostimulatory approach has the potential to gain access to a variety of markets. In the cancer arena, Juvaris' technology could impact melanoma as well as prostate, breast, lung, and colon cancer. Other applications include antibiotic−resistant bacteria, viral infections such as herpes and HIV, and fungal and parasitic diseases. Juvaris' products also have potential in the companion animal market, which the company says is about $3 billion per year and growing at an annual rate of 10%. Despite this sizeable market, there are few effective treatments for cancers and infectious diseases. *JuvImmune* could also be used in livestock to

prevent a variety of respiratory diseases collectively referred to as shipping fever.

The wide potential is promising for Juvaris, but there is no shortage of competition for these markets. There is a broad consensus that a specific group of receptors on the surfaces of dendritic cells−−called Toll−like receptors (TLRs)−−are critical to activating the immune response. When dendritic cells find an invader, they chew it up into components called antigens, which the cells then present to T−cells and other immune system cells, prompting an adaptive immune response tailored to the specific organism. Activation of TLRs is a key element to this cascade of events.

Many pharmaceutical companies have research programs aimed at activating TLRs. A common approach is using cytosine guanosine phosphate (CpG), which triggers TLR−9. **Coley Pharmaceutical Group Inc.**, **Dynavax Technologies Corp.**, and a number of other companies are pursuing CpGs.

Another competing approach to TLR activation is monophosphoryl lipid A (MPL). MPL is a key component in a number of vaccines currently in development by **GlaxoSmithKline PLC**, which gained access to the technology through a 2005 acquisition of Corixa Corp. [W#200510091] **3M Co.** has a line of immune response modifiers that affect TLRs, including a dermatology product called *Aldara*, which is FDA approved for the treatment of actinic keratosis (a skin condition that can be pre−cancerous), genital and perianal warts, and a form of skin cancer known as superficial basal cell carcinoma. "There are lots of approaches to try to drive the immune response," says Cleary. He adds that *JuvImmune* and *JuvaVax* also likely stimulate TLR receptors, but the company hasn’t yet determined which ones.

Juvaris has several advantages going for it, according to Cleary. *JuvaVax* is very good at eliciting responses from T−cells−−in particular, it induces a response by a subset of T−cells called CD8+ T−cells, which are critical to the immune response against viruses, certain kinds of bacteria, and tumor cells. Few other vaccine technologies induce a CD8+ T−cell response, he says. *JuvaVax* has also been shown to be effective in immunocompromised mice, raising the intriguing possibility that it could be used in immunocompromised patients, such as those with HIV or certain forms of cancers.

JuvImmune also appears to stimulate mucosal immunity, which means it has the potential to be given orally rather than as an injection. "Imagine how it would change the vaccine industry if you could give therapeutic vaccines orally," says Cleary.

Valentis’ experience with the technology is a boon to Juvaris, because it can make use of the data previously collected when it was being pursued as a gene therapy delivery vehicle. "The material has been in human clinical trials, which allows us to take advantage of all the development time that Valentis put in to create the manufacturing methods and optimize components for getting the DNA into cells. That’s the key element; once the DNA gets into particular immune cells, it can activate the immune system very efficiently," says John Warner, who is Juvaris’ chief scientific officer. In fact, Juvaris has drawn on Valentis’ expertise, having hired seven of Valentis’ former employees. "We have something like 90 years of cumulative experience with the technology. We know it very well," says Cleary.

The strengths of Juvaris' technology have already enticed a variety of academic collaborators as well as some interest from industry. Juvaris does not yet have any corporate partners, though it is engaged in a number of discussions. "A lot of folks have come to us and said that they would like to take *JuvImmune* and combine it with their candidate vaccine and see if there's a benefit," says Cleary.

Juvaris has raised $16.5 million to date, including a $12 million Series A round commitment in December 2006 from Kleiner Perkins Caufield & Byers' Pandemic & Biodefense Fund. [W#200730017] "Kleiner Perkins Caufiled & Byers was also instrumental in directing our program for prophylactic vaccines and adjuvants where the return on investment is far more rapid than cancer programs," says Cleary.

Juvaris does not have the resources to progress into late−stage clinical trials, so instead the company plans to achieve positive results in early−stage studies with prophylactic vaccines (the *JuvaVax* line) and then recruit corporate partners to complete development.

Cleary anticipates a different strategy with *JuvImmune*, which won't be disease specific. "The same vial of *JuvImmune* will treat multiple diseases," he says. For *JuvImmune*, he hopes to recruit a much later stage marketing partner among one of the big players in the pharmaceutical field. "We see it as a three− to five−year plan before the company is either acquired outright, or is in a position to go public."

Cleary is confident that the upcoming clinical trials will produce favorable results, but he worries that even strong results may not be enough to attract corporate partners to finance late−stage clinical development. "I don't think it's about the technology or the clinical outcomes. The question is, will the clinical results be favorable enough to bridge the gap between where we are now and the IPO or merger market, without having to do series B, C, or D funding?" says Cleary. The key will likely be Phase II clinical results, which the company anticipates it will generate in 2009. "Strong Phase II data is where the bar is now," says Cleary.−− ***Jim Kling***